# Pharmacologic Treatment of Tardive Dyskinesia:
## A Meta-Analysis and Systematic Review

Bekir B. Artukoglu, MD[a,*]; Fenghua Li, MS[a]; Natalia Szejko, MD[b]; and Michael H. Bloch, MD, MS[a,c]


### ABSTRACT

***Objective:*** To examine the efficacy of pharmacologic treatments for tardive dyskinesia (TD).

***Data Sources:*** PubMed was searched on December 12, 2017, for randomized, placebo-controlled trials examining the treatment of TD using the search terms (*drug-induced dyskinesia* OR *tardive dyskinesia*) AND (*psychotic disorders* OR *schizophrenia*).

***Study Selection:*** Studies were included if they examined tardive dyskinesia treatment as the primary outcome and were randomized and placebo-controlled trials.

***Data Extraction:*** The effect size (standard mean difference) of improvement (compared to placebo) stratified by medication class is reported for each of the trials included in this systematic review. A meta-analysis was conducted utilizing a fixed-effects model.

***Results:*** Vitamin E was associated with significantly greater reduction in TD symptoms compared to placebo (standardized mean difference [SMD] = 0.31 ± 0.08; 95% CI, 0.16 to 0.46; $z = 4.1$; $P < .001$). There was significant evidence of publication bias in vitamin E studies (Egger test: $P = .02$). Shorter duration of treatment and lower dose of vitamin E were significantly associated with greater measured treatment benefit. Vitamin $B_6$ was associated with significantly greater reduction in TD symptoms compared to placebo (SMD = 1.41 ± 0.22; 95% CI, 0.98 to 1.85; $z = 6.4$; $P < .001$) in 2 trials conducted by the same research group. Vesicular monoamine transporter 2 (VMAT2) inhibitors demonstrated significant benefit on tardive dyskinesia symptoms compared to placebo (SMD = 0.63 ± 0.11; 95% CI, 0.41 to 0.85; $z = 5.58$; $P < .005$). Amantadine was associated with significantly greater score reduction compared to placebo (SMD = 0.46 ± 0.21; 95% CI, 0.05 to 0.87; $z = 2.20$; $P < .05$). Calcium channel blockers were not associated with significantly greater score reduction compared to placebo (SMD = 0.31 ± 0.33; 95% CI, −0.34 to 0.96; $z = 0.93$; $P = .35$).

***Conclusions:*** Data from multiple trials suggests that VMAT2 inhibitors, vitamin E, vitamin $B_6$, and amantadine may be effective for the treatment of TD. Evidence of publication bias and a significant negative association of dose and duration of treatment with measured efficacy suggest that the benefits of vitamin E in TD may be overstated. Head-to-head trials are needed to compare the efficacy and cost-effectiveness of pharmacologic agents for TD.


*J Clin Psychiatry 2020;81(4):19r12798*

***To cite:*** Artukoglu BB, Li F, Szejko N, et al. Pharmacologic treatment of tardive dyskinesia: a meta-analysis and systematic review. *J Clin Psychiatry*. 2020;81(4):19r12798.

***To share:*** https://doi.org/10.4088/JCP.19r12798



[a]Yale Child Study Center, New Haven, Connecticut

[b]Department of Neurology, Medical University of Warsaw, Warsaw, Poland

[c]Department of Psychiatry, Yale University, New Haven, Connecticut

**Corresponding author:* Bekir B. Artukoglu, MD, Yale Child Study Center, PO Box 207900, New Haven, CT 06520-7900 (bekir.artukoglu@yale.edu).

Antipsychotic medications are the first-line treatment for psychotic disorders. Efficacy of antipsychotic medication has been established through meta-analysis of randomized controlled trials.[1,2] Antipsychotic agents are also effective for and are often utilized to treat mania,[3] anxiety,[4,5] depression,[6–10] and childhood aggression.[11–13] Given the broadening indications for antipsychotic medication, use of these medications has increased dramatically over the last two decades. One study[14] indicates that as many as 1.6% of the American population were exposed to antipsychotics in 2013.

Side effects limit the tolerability of antipsychotic medications for many patients. Extrapyramidal symptoms (EPS) are antipsychotic-induced side effects that are caused by dopaminergic blockade at the nigrostriatal pathway.[15,16] Early-onset EPS such as akathisia, dystonia, and parkinsonism are usually seen in the first few weeks of antipsychotic exposure. Tardive dyskinesia (TD) is a late-onset extrapyramidal side effect that is estimated to develop in 20%–50% of patients on long-term antipsychotic treatment.[17] Tardive dyskinesia involves orofacial stereotypies including grimacing, chewing, and tongue movements. Tardive dyskinesia can cause significant disability and medication nonadherence and is associated with economic consequences.[18–21] Tardive dyskinesia is less commonly seen with atypical antipsychotics,[22] but it has been reported to be caused by many of these agents as well.[23] Although the exact etiologic mechanism of TD is unknown, it remains clear that chronic $D_2$ receptor antagonism is involved in its pathogenesis.[24,25]

There are currently many clinical interventions that are utilized to reduce TD symptoms when they occur. Discontinuing antipsychotics, when possible, often reduces symptoms of TD. However, TD can persist even after antipsychotic discontinuation.[26–29] Reduced dosage of a typical antipsychotic or switching to an atypical antipsychotic are some of the options for clinicians. These treatment strategies are supported by randomized controlled trials.[30,31] Many augmentation agents have been examined regarding efficacy for antipsychotic-induced TD. Two vesicular monoamine transporter 2 (VMAT2) inhibitors, valbenazine and deutetrabenazine, have been recently approved by the US Food and Drug Administration (FDA) for the treatment of TD.[32,33] Meta-analyses and systematic reviews have compared the efficacy of different compounds for TD, but these reviews have not been updated in over a decade, during which

**Clinical Points**

- Tardive dyskinesia (TD), an oral and facial movement disorder that is a potential side effect of antipsychotic treatment, can cause significant disability and medication nonadherence.
- Vitamin E was associated with significantly greater reduction in TD symptoms compared to placebo per meta-analysis, although its benefits may be inflated by publication bias.
- Vesicular monoamine transporter 2 (VMAT2) inhibitors have strong evidence of efficacy in TD based on the results of several large randomized controlled trials.

several studies and advances have taken place.[26–28] The goal of this systematic review and meta-analysis is to examine the efficacy of different agents used in the treatment of TD.

## METHODS

### Search Strategy for Identification of Studies

Two reviewers (B.B.A., M.H.B.) searched the electronic database of PubMed on December 12, 2017, for relevant studies using the search ((*Dyskinesias[mesh]* OR *Dyskinesia, Drug-Induced[mesh]* OR (*abnormal** near *movement** *near disorder**) OR (*involuntary** near *movement**)) AND (*Psychotic Disorders[mesh]* OR *Schizophrenia[mesh]*)) OR *tardive dyskinesia[mesh]* OR (*tardive* near (*dyskine** or *diskine**)). The search was restricted using the "randomized controlled trial" filter. We additionally used the same search strategy and limited it using the "review" filter. These studies were further reviewed for additional relevant citations.

### Selection of Studies

The titles and abstracts of studies obtained by this search strategy were examined by two reviewers (B.B.A., M.H.B.) to determine inclusion in this meta-analysis. Any discrepancies were resolved by the two reviewers. Eligibility for the study was based upon analysis of the full articles for the following criteria: they needed to (1) examine tardive dyskinesia treatment effect as primary outcome, (2) be randomized, and (3) be placebo-controlled. Discontinuation studies or studies that involved duplication of data from other included trials were excluded. Head-to-head studies without a placebo control were excluded. We also excluded trials examining subjects who did not already have TD (eg, studies comparing the likelihood of two different antipsychotics to cause TD or examining prevention of TD when an antipsychotic was started). Crossover trials were included.

### Meta-Analytic Procedures

Data were extracted by independent reviewers (B.B.A., M.H.B.) on specially designed Microsoft Excel spreadsheets. Our primary outcome measure was the efficacy of different medications for the treatment of TD. The Abnormal Involuntary Movement Scale (AIMS) and the Extrapyramidal Symptom Rating Scale (ESRS) Dyskinetic Movement Subscale were used to gather information on the severity of TD.[34,35] Reviewers also gathered data on trial design, maximum daily medication dose, number of participants in active group, number of participants in placebo group, and other relevant attributes and results of the studies. Study quality was assessed using the Jadad scale[36] and Cochrane Risk of Bias Table.[37] A study was considered to have a low risk of bias if it satisfied the first 3 items and there were no concerns related to the remaining 3 domains. Studies were considered to have a moderate risk of bias when the answers to 1 or 2 domains were "Unclear" or "No" and a high risk of bias was when the answers to 3 or more domains were "Unclear" or "No." Disagreement among reviewers was mitigated through discussion and the procurement of more information from the study investigators if possible. When information about the efficacy of a medication for the treatment of TD was not available in the original articles, the corresponding author was contacted for further information.

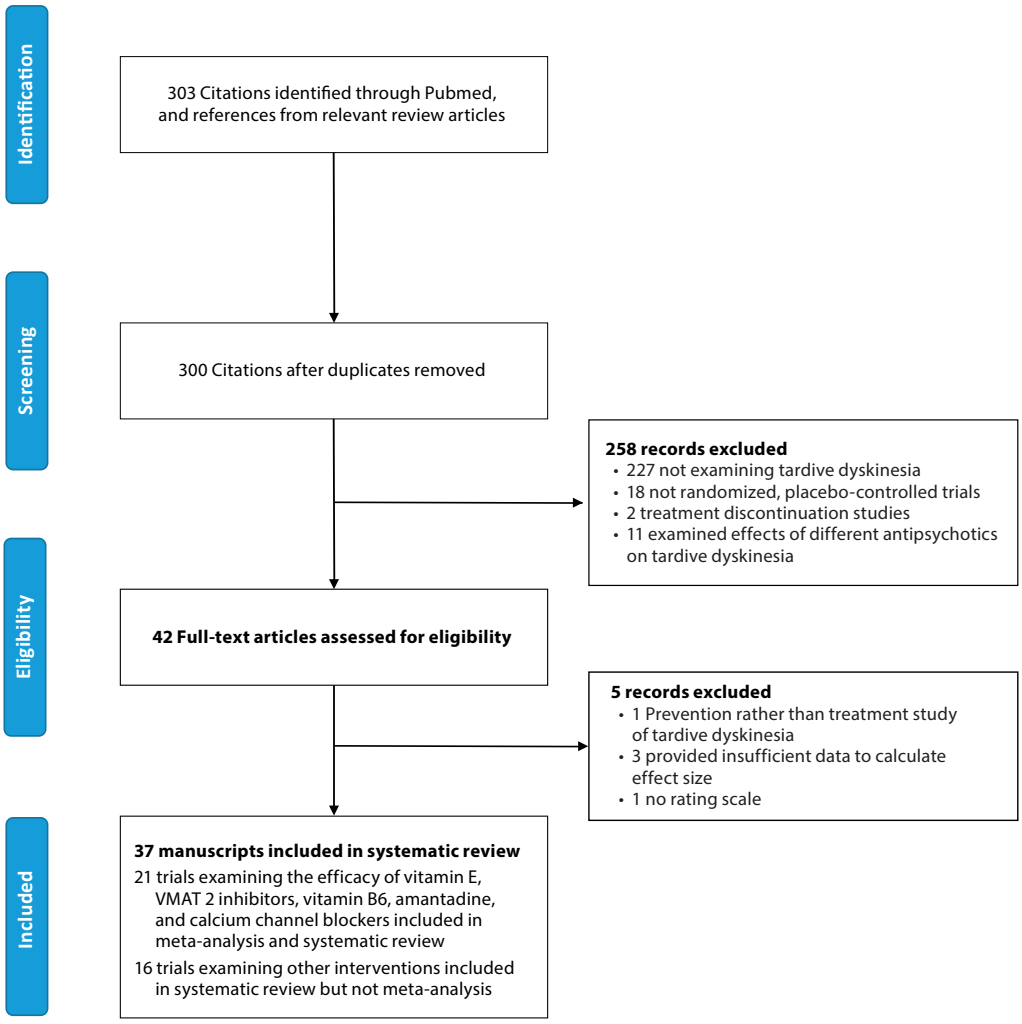
All statistical analyses were completed in Comprehensive Meta-Analysis Version 3 (Biostat; Englewood, New Jersey).[38] Our primary outcome of interest was TD severity. Standardized mean difference (SMD) of the difference between active treatment and placebo conditions on TD was used as the primary outcome for the meta-analysis. Standardized mean difference was selected as an outcome over weighted mean difference as investigators used different rating scales to assess TD severity. Studies were stratified by the type of medication (vitamin E, vitamin $B_6$, VMAT2 inhibitors, anticholinergics, and calcium channel blockers). All other medication trials were treated as different categories. A fixed-effects model was used as the primary method for meta-analysis as we were concerned about the possibility of publication bias in the literature. When there is significant publication bias, fixed-effects models are generally considered more conservative than random-effects models, as fixed-effects models give less weight to smaller studies that are more likely to be affected by publication bias. Publication bias was assessed by plotting the effect size against standard error for each included trial (ie, funnel plot). In addition, publication bias was statistically tested by the Egger test. We were able to examine publication bias and conduct stratified subgroup analyses and meta-regressions only for vitamin E trials because all other agents were examined in too few trials ($\kappa \leq 3$). Stratified subgroup analysis and meta-regression were used to examine the effects of dose and duration in studies of vitamin E. All subgroup analyses were performed using fixed-effects models. Our threshold for statistical significance was $P < .05$ for the primary analysis. Heterogeneity was assessed using the Cochran $Q$ and $I^2$ tests.

## RESULTS

### Included Trials

Figure 1 depicts the selection of trials for inclusion in this systematic review and meta-analysis. A total of 303 references were identified in PubMed and from relevant review articles. A total of 37 randomized controlled clinical trials were

Figure 1. PRISMA Diagram for Selection of Studies in Meta-Analysis




eligible for potential inclusion once the titles, abstracts, and full texts (when necessary) were reviewed.[39–75] Three trials studied the efficacy of VMAT2 inhibitors (tetrabenazine, deutetrabenazine, and valbenazine), 15 trials investigated the efficacy of vitamin E, and 2 studies investigated vitamin $B_6$. Three trials studied the efficacy of amantadine, and 2 trials investigated calcium channel blockers (diltiazem and nifedipine). Individual trials also investigated the efficacy of *Ginkgo biloba*, levetiracetam, ethyl-EPA, α-methyldopa, biperiden, cerulitide, galantamine, insulin, melatonin, naltrexone, piracetam, conjugated estrogens, reserpine, selegiline, and sulpiride. The characteristics of included trials are presented in Table 1.

## Vitamin E

Fifteen trials including 502 subjects examined the effects of vitamin E on TD. The forest plot in Figure 2 depicts the effect of vitamin E on the severity of TD symptoms compared to placebo in randomized controlled trials. Vitamin E was associated with significantly greater score reduction in TD symptoms compared to placebo (SMD = 0.31 ± 0.08; 95% CI, 0.16 to 0.46; $z = 4.1$, $P < .001$). There was evidence of heterogeneity between trials (test for heterogeneity: $\chi^2_{14} = 33.3$, $P < .005$, $I^2 = 58\%$). Figure 3 depicts a funnel plot examining publication bias. There is significant asymmetry in the funnel plot suggesting possible publication bias. The Egger test reached statistical significance (Egger intercept = 2.4 ± 0.94; 95% CI, 0.40 to 4.5; $P = .02$). An increased dose of vitamin E (1,600 IU/d: SMD = 1.16 ± 0.09; 95% CI, −0.01 to 0.33; $z = 1.8$, $P = .07$) was associated with significantly less symptom improvement (test for subgroup differences $\chi^2_1 = 11.7$, $P = .001$) compared to placebo compared to lower dose vitamin E trials (1,200 IU/d: SMD = 0.77 ± 0.15; 95% CI, 0.47 to 1.1; $z = 5.0$, $P < .001$). Longer duration of treatment with vitamin E was also associated with reduced benefit compared to placebo (coefficient = 0.57, standard error of the mean [SEM] = 0.16; 95% CI, 0.26 to 0.89; $z = 3.58$, $P < .001$).

## Vitamin $B_6$

Only 2 trials[41,42] from the same investigator group that included a total of 51 subjects examined the effects of vitamin

**Table 1. Characteristics of Included Trials Included in the Meta-Analysis[a]**

| Study Characteristics | | | | | | Cochrane Risk of Bias Table | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Agent | Dose | Duration (wk) | Sample Size (Active:Control) | Jadad Score | Random Sequence Generation (Selection Bias) | Allocation Concealment (Selection Bias) | Blinding of Participants And Personnel (Performance Bias) | Blinding of Outcome Assessment (Detection Bias) (Clinician-Reported Outcomes) | Incomplete Outcome Data Addressed (Attrition Bias; Short-Term Outcomes [2–6 wk]) | Incomplete Outcome Data Addressed (Attrition Bias; Longer-Term Outcomes [> 6 wk]) | Selective Reporting (Reporting Bias) |
| **VMAT2 Inhibitors** | | | | | | | | | | | | |
| Hauser et al 2017[40] | Valbenazine | 40, 80 mg | 6 | 70:79:76 | 5 | + | + | + | + | + | + | + |
| Fernandez et al 2007[43] | Deutetrabenazine | 36 mg | 12 | 58:59 | 5 | + | + | + | + | + | + | + |
| Jankovic 1982[69] | Tetrabenazine | 200 mg | 4 | 4:4 | 3 | ? | ? | ? | ? | + | + | + |
| **Vitamin E** | | | | | | | | | | | | |
| Adler et al 1993[44] | Vitamin E | 1,600 IU | 10 | 16:12 | 4 | + | + | + | + | − | − | + |
| Adler et al 1998[53] | Vitamin E | 1,600 IU | 36 | 16:12 | 3 | ? | + | + | ? | + | + | + |
| Adler et al 1999[45] | Vitamin E | 1,600 IU | 48 | 49:55 | 3 | + | + | + | ? | − | − | + |
| Akhtar et al 1993[46] | Vitamin E | 1,200 IU | 4 | 17:15 | 5 | ? | ? | + | + | + | − | + |
| Bridler 2001[68] | Vitamin E | 1,600 IU | 48 | 76:77 | 2 | ? | ? | ? | ? | − | − | ? |
| Dabiri et al 1994[47] | Vitamin E | 1,200 IU | 12 | 5:6 | 4 | ? | + | + | + | + | + | + |
| Egan et al 1992[48] | Vitamin E | 1,600 IU | 6 | 18:18 | 2 | ? | ? | + | ? | − | − | + |
| Elkashef et al 1990[49] | Vitamin E | 1,200 IU | 4 | 8:8 | 3 | ? | ? | + | + | + | + | + |
| Lam et al 1994[50] | Vitamin E | 1,200 IU | 6 | 12:12 | 2 | ? | + | + | ? | − | − | + |
| Lohr et al 1988[39] | Vitamin E | 1,200 IU | 4 | 27:27 | 2 | ? | ? | ? | ? | + | + | + |
| Lohr and Caligiuri 1996[54] | Vitamin E | 1,600 IU | 8 | 17:18 | 5 | ? | ? | + | + | + | + | + |
| Schmidt et al 1992[52] | Vitamin E | 1,200 IU | 2 | 19:19 | 2 | + | ? | + | ? | − | X | + |
| Shriqui et al 1992[51] | Vitamin E | 1,200 IU | 6 | 27:27 | 4 | ? | ? | + | + | − | − | + |
| **Vitamin B6** | | | | | | | | | | | | |
| Lerner et al 2001[42] | Vitamin $B_6$ | 400 IU | 4 | 15:15 | 3 | ? | ? | + | ? | − | − | + |
| Lerner et al 2007[41] | Vitamin $B_6$ | 1200 IU | 12 | 36:36 | 3 | ? | ? | + | + | + | + | + |
| **Anticholinergics** | | | | | | | | | | | | |
| Silver et al 1995[66] | Amantadine | 200 mg | 2 | 9:9 | 3 | ? | ? | + | + | − | X | + |
| | Biperiden | 2 mg | 2 | 9:9 | | | | | | | | |
| Angus et al 1997[73] | Amantadine | 300 mg | 2 | 16:16 | 5 | ? | ? | + | + | + | + | + |
| Pappa et al 2010[72] | Amantadine | 100 mg | 2 | 22:22 | 5 | ? | ? | + | ? | + | + | + |
| **Calcium Channel Blockers** | | | | | | | | | | | | |
| Suddath et al 1991[67] | Nifedipine | 90 mg | 4 | 4:4 | 4 | ? | ? | + | + | ? | − | + |
| Loonen et al 1992[75] | Diltiazem | 60 mg | 3 | 17:17 | 5 | + | ? | + | ? | + | X | + |
| **Other Agents** | | | | | | | | | | | | |
| Caroff et al 2007[55] | Galantamine | 24 mg | 12 | 32:26 | 3 | ? | ? | + | + | + | + | + |
| Emsley et al 2006[56] | Ethyl-EPA | 2 g | 12 | 39:38 | 5 | + | + | + | + | + | + | + |
| Glazer et al 1985[57] | Conjugated estrogens | 1.25 mg | 3 | 5:5 | 5 | ? | ? | + | + | + | X | + |
| Goff et al 1993[58] | Selegiline | 10 mg | 6 | 12:16 | 5 | ? | ? | + | + | + | X | + |
| Wonodi et al 2004[59] | Naltrexone | 200 | 4 | 9:9 | 3 | ? | ? | + | ? | + | + | + |
| | Naltrexone after 4-wk clonazepam stabilization | 200 mg (naltrexone), 0.5 mg (clonazepam) | | 14:14 | | | | | | | | |

*(continued)*

**Table 1 (continued).**

| Study | Agent | Study Characteristics: Dose | Duration (wk) | Sample Size (Active:Control) | Jadad Score | Cochrane Risk of Bias Table: Random Sequence Generation (Selection Bias) | Allocation Concealment (Selection Bias) | Blinding of Participants And Personnel (Performance Bias) | Blinding of Outcome Assessment (Detection Bias) (Clinician-Reported Outcomes) | Incomplete Outcome Data Addressed (Attrition Bias; Short-Term Outcomes [2–6 wk]) | Incomplete Outcome Data Addressed (Attrition Bias; Longer-Term Outcomes [> 6 wk]) | Selective Reporting (Reporting Bias) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Huang et al 1981[60] | Reserpine | 1.5 mg | 2 | 10:10 | 4 | ? | ? | + | + | – | X | + |
| | α-Methyldopa | 1,500 mg | 2 | 10:10 | | | | | | | | |
| Kojima et al 1992[61] | Cerulitide | 0.008 mg/kg | 3 | 33:33 | 3 | + | ? | + | + | – | – | + |
| Libov et al 2007[62] | Piracetam | 4,800 mg | 4 | 31:31 | 4 | + | + | + | + | + | + | + |
| Mouret et al 1991[63] | Insulin | 10 units | 12 | 10:10 | 4 | + | + | + | + | + | + | + |
| Shamir et al 2001[64] | Melatonin | 10 mg | 6 | 22:22 | 5 | + | + | + | + | + | + | + |
| Schwartz et al 1990[65] | Sulpiride | 600 mg | 4 | 15:15 | 2 | ? | ? | – | – | + | + | + |
| Thaker et al 1990[70] | Clonazepam | 4.5 mg | 12 | 19:19 | 4 | ? | ? | + | + | + | + | + |
| Woods et al 2008[74] | Levetiracetam | 3,000 mg | 12 | 25:25 | 5 | + | + | + | ? | + | + | + |
| Zhang et al 2010[71] | *Ginkgo biloba* | 240 mg | 12 | 78:79 | 3 | ? | ? | + | ? | + | + | + |

[a]The table shows the number of active and control subjects, medication used, dose and duration of treatment, Jadad score, and the Cochrane Risk of Bias Table data for each study.
Abbreviations: EPA = ethyl-eicosapentaenoic acid, VMAT2 = vesicular monoamine transporter 2.
Key:
– High risk of bias
? Unclear risk of bias
+ Low risk of bias
X Not applicable—less than 6 wk

$B_6$ on TD. Figure 2 depicts the effects of vitamin $B_6$ on the severity of TD symptoms compared to placebo in randomized controlled trials. Vitamin $B_6$ was associated with significantly greater reduction in TD symptoms compared to placebo (SMD = 1.41 ± 0.22; 95% CI, 0.98 to 1.85; $z = 6.4$, $P < .001$). There was no significant evidence of heterogeneity between trials (test for heterogeneity: $\chi^2_1 = 0.02$, $P = .88$, $I^2 = 0\%$).

### VMAT2 Inhibitors

Three trials[40,43,69] including 346 subjects examined the effects of VMAT2 inhibitors on TD. Figure 2 depicts the effect of VMAT2 inhibitors on the severity of TD symptoms compared to placebo in randomized controlled trials. VMAT2 inhibitors were associated with significantly greater score reduction compared to placebo (SMD = 0.63 ± 0.11; 95% CI, 0.41 to 0.85; $z = 5.58$, $P < .005$). Valbenazine (SMD = 0.72 ± 0.14; 95% CI, 0.44 to 0.99; $z = 5.02$, $P < .001$), deutetrabenazine (SMD = 0.40 ± 0.19; 95% CI, 0.04 to 0.77; $z = 2.2$, $P < .05$), and tetrabenazine (SMD = 3.23 ± 1.07; 95% CI, 1.12 to 5.33; $z = 3.01$, $P < .005$) demonstrated significant benefit compared to placebo in individual trials. There was no significant evidence of heterogeneity between trials (test for heterogeneity: $\chi^2_4 = 10.6$, $P = .032$, $I^2 = 62.2\%$).

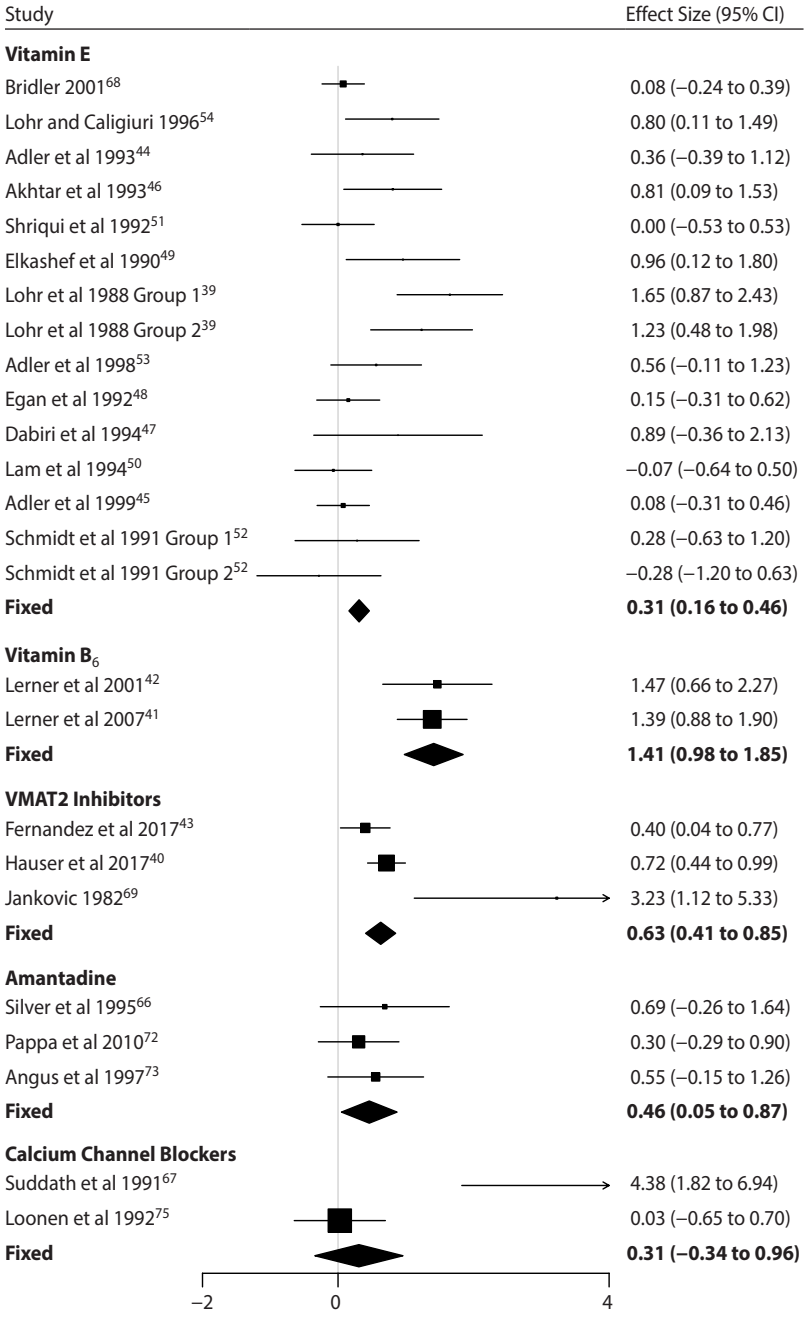
### Anticholinergics

One trial[66] including 9 subjects examined the effects of amantadine and biperiden on TD. Two different trials[72,73] including 38 subjects also examined the effects of amantadine on TD. Figure 2 depicts the effect of anticholinergic medications on the severity of TD symptoms compared to placebo in randomized controlled trials. Amantadine was associated with significantly greater reduction in TD symptoms compared to placebo (SMD = 0.46 ± 0.21; 95% CI, 0.05 to 0.87; $z = 2.20$, $P < .05$). There was no significant evidence of heterogeneity between amantadine trials (test for heterogeneity: $\chi^2_2 = 0.6$, $P = .76$, $I^2 = 0\%$). A 2-week randomized, double-blind, placebo-controlled crossover trial[66] of amantadine (200 mg) and biperiden (4 mg) in 9 subjects revealed a significant and similar effect of treatment for both amantadine (mean ± SD = 1.78 ± 2.22) and biperiden (mean ± SD = 1.67 ± 1.66). This study had moderate risk of bias according to the Cochrane risk of bias tool; incomplete outcome data were not addressed, as random sequence generation and allocation concealment were unclear.

### Calcium Channel Blockers

Two trials[67,75] including 21 subjects examined the effects of CCBs on TD. Figure 2 depicts the effect of

**Figure 2. Efficacy of Pharmacologic Agents for Tardive Dyskinesia[a]**




[a]This forest plot depicts the treatment benefit for tardive dyskinesia compared to placebo in pharmacologic agents with > 1 included trial (vitamin E, vitamin $B_6$, VMAT2 inhibitors, amantadine, and calcium-channel blockers). Boldface values are summaries for groups.
Abbreviation: VMAT2 = vesicular monoamine transporter 2.

CCBs on the severity of TD symptoms compared to placebo in randomized controlled trials. CCBs were not associated with significantly greater score reduction compared to placebo (SMD = 0.31 ± 0.33; 95% CI, −0.34 to 0.96; $z = 0.93$, $P = .35$). Nifedipine (SMD = 4.38 ± 1.30; 95% CI, 1.83 to 6.94; $z = 3.36$, $P < .001$) demonstrated a significant benefit compared to placebo, whereas diltiazem (SMD = 0.03 ± 0.34; 95% CI, −0.65 to 0.70; $z = 0.08$, $P = .94$) failed to do so in individual trials. There was significant evidence of heterogeneity between the 2 trials (test for heterogeneity: $\chi^2_1 = 10.4$, $P < .005$, $I^2 = 90\%$).

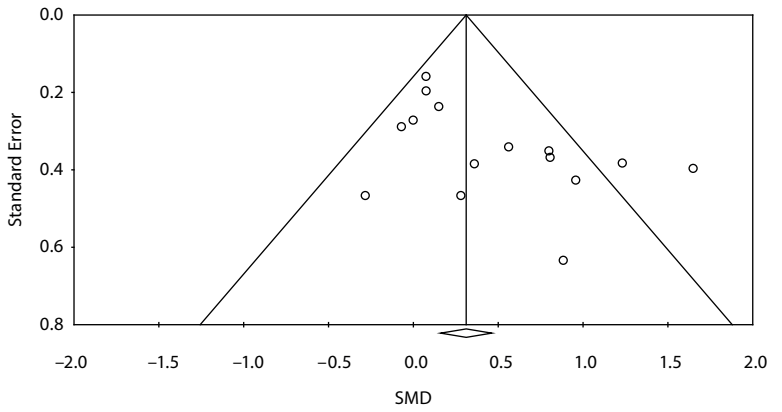
The presence of voltage-sensitive calcium channels in the central nervous system (CNS) and dyskinetic effects of calcium channel blockers (CCBs) in animal studies[76,77] may explain how the dihydropyridine CCB nifedipine may improve TD symptoms. A randomized, controlled crossover trial[67] showed that 4 weeks of nifedipine treatment (90 mg) led to a statistically significant decrease in total AIMS scores by a mean ± SEM of 57.2% ± %9.0) in 4 subjects. In a double-blind, placebo-controlled, crossover study[75] in 17 patients, 3 weeks of treatment with the non-dihydropyridine CCB diltiazem (60 mg) was not associated with a statistically significant reduction in the total AIMS score compared with the placebo treatment. Both studies on calcium channel blockers had moderate risk of bias due inadequate information on randomization process and blinding of outcome assessment.

## Other Agents Investigated in Individual Studies

Figure 4 depicts the effects of all the medications that have been used to treat TD in controlled trials. Sixteen trials that examined separate individual medications were evaluated for qualitative synthesis. *Ginkgo biloba*, levetiracetam, ceruletide, insulin, melatonin, piracetam, conjugated estrogens, selegiline, and sulpiride demonstrated significant benefit compared to placebo in individual trials. Ethyl-eicosapentaenoic acid (ethyl-EPA), galantamine, reserpine, α-methyldopa, and naltrexone failed to differentiate from placebo in individual trials. The methodological quality of many of the trials was poor as depicted in Table 1, and their results have not been replicated. Although all the studies were placebo controlled, 1 study,[65] a sulpiride trial, was single blind and 1 article[39] did not provide enough information on the blinding of the trial. Five studies were properly randomized, whereas 11 manuscripts did not provide sufficient information about the random sequence generation. Associations with dose or duration were not examined in any of the individual trials. These trials were generally single-site studies with small sample sizes and thus had inadequate power to detect even moderate treatment benefits.

**Ginkgo biloba.** The antioxidant properties of the free radical scavenger EGb-761, a *Ginkgo biloba* extract, have implications for its use in TD, based on the theory that free radicals play a role in TD pathogenesis.[71] A randomized,

**Figure 3. Funnel Plot Examining Potential Publication Bias in Vitamin E Trials for Tardive Dyskinesia[a]**




[a]This figure depicts a funnel plot examining publication bias in vitamin E trials. Vitamin E was associated with significantly greater reduction in tardive dyskinesia symptoms compared to placebo (SMD = 0.31 ± 0.08; 95% CI, 0.16 to 0.46; $z = 4.1$; $P < .001$) but also funnel plot asymmetry suggesting publication bias (Egger test: $P = .02$).
Abbreviations: SMD = standardized mean difference.

double-blind, placebo controlled, 12-week trial[71] was conducted to compare the effects of 240 mg/d EGb-761 (n = 78) and placebo (n = 79) on TD symptoms. EGb-761 treatment significantly decreased the AIMS total score in patients with TD compared to those who were given a placebo (2.13 ± 1.75 vs −0.10 ± 1.69; $P < .0001$), with 40 (51.3%) and 4 (5.1%) patients achieving response in the EGb-761 and placebo treatment groups, respectively. This study had a Jadad score of 3 and a moderate risk of bias according to the Cochrane risk of bias tool to due inadequate information on randomization process and blinding of outcome assessment.

***Levetiracetam.*** While its mechanism of action is unclear, levetiracetam has a binding site on CNS membranes known as synaptic vesicle protein 2A and is known to exhibit antidyskinetic properties in animal models and open-label studies in humans.[78] In a double-blind, randomized study,[74] 25 patients were assigned to 500–3000 mg/d of levetiracetam and 25 patients to placebo for 12 weeks. Mixed regression models revealed that AIMS total scores declined 43.5% from baseline in the levetiracetam group compared to 18.7% for placebo ($P = .022$). This study had a high Jadad score of 5 and low risk of bias according to the Cochrane risk of bias tool.

***Melatonin.*** Melatonin is hypothesized to improve TD symptoms through detoxification of free radicals[74] or due to its ability to reduce excitability of nigrostriatal neurons and to modulate dopaminergic neurotransmission in the rat striatum.[79,80] Melatonin was evaluated in a double-blind, placebo controlled, crossover study design in 22 subjects for 6 weeks.[64] Compared with placebo, 10 mg/d of melatonin led to significant decrease in AIMS scores (2.45 ± 1.92),which was a large effect size. This study had a low risk of bias according to the Cochrane risk of bias tool and had the highest possible Jadad score of 5.

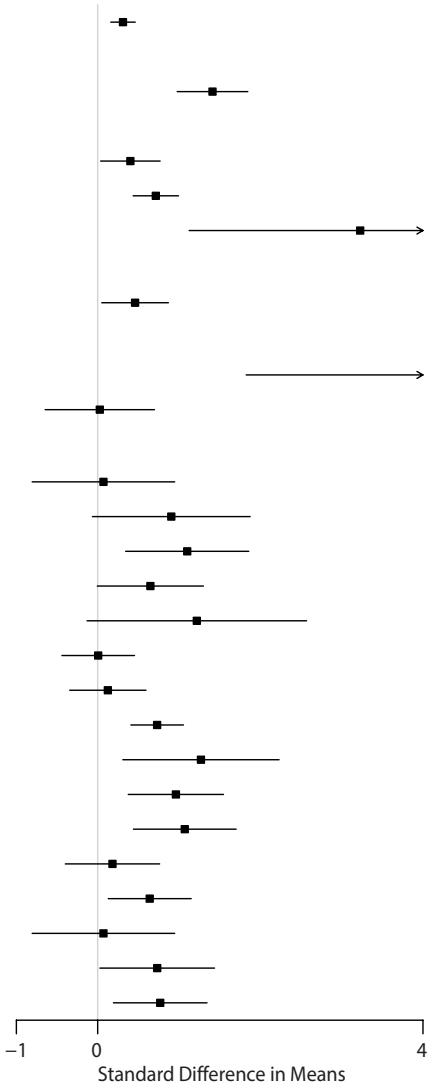
***Piracetam.*** Piracetam is hypothesized to reduce TD symptoms due to its antioxidant properties or through its ability to increase the acetylcholine receptor density.[81–83] A 4-week, double-blind, placebo-controlled, crossover study[62] was conducted to examine the effects of a piracetam trial (4,800 mg/d) on the TD symptoms. Symptoms of TD during piracetam treatment improved, decreasing by 3 points, while in the placebo group the symptoms deteriorated, decreasing by 0.2 points. This study had a low risk of bias according to the Cochrane risk of bias tool and had a high Jadad score of 4.

***Insulin.*** It can be argued that dopaminergic hypersensitivity is due to energy-dependent processes such as dopamine receptor synthesis and that a reduction in glucose availability with insulin would target the metabolically hyperactive structures in TD.[63] A placebo-controlled, randomized, double-blind, parallel-group study[63] tested the efficacy of a total of 20 subcutaneous, 10 units standard insulin injections in 90 days. Ten subjects received insulin and 10 received placebo, and statistical analysis, performed using analysis of variance tests for repeated measures, validated the effect of insulin at $P < .001$ ($F$ value = 24.53), whereas no statistically significant change was found in the placebo-treated group ($F$ value = 1.81). This trial was associated with a low risk of bias according to the Cochrane risk of bias tool and had a high Jadad score 4.

***Ceruletide.*** Animal studies[84] have revealed that ceruletide may have central effects on dopaminergic neurons such as the suppression of intracerebral dopamine metabolism in the rat caudate nucleus and putamen; these effects may explain its usefulness in the treatment of TD and related movement disorders. A double-blind, placebo-controlled, matched-pairs study design[61] was used to evaluate the effectiveness of 8 weeks of once-weekly intramuscular injection of ceruletide (0.8 pg/kg) in TD treatment. Analyses were performed on the 33 pairs; a moderate-to-marked improvement rate of 42.4% was found in the ceruletide group as compared with a 9.1% improvement rate in the placebo group. This study had a moderate risk of bias and authors did not provide enough information on allocation concealment and the incomplete outcome data.

***Reserpine and α-methyldopa.*** Dopamine-depleting effects of reserpine and dopa-decarboylase inhibitory function of α-methyldopa suggest that these medications may improve TD symptoms.[85,86] Thirty subjects participated in a double-blind, controlled, randomized study[60] comparing reserpine (doses of 0.75–1.5 mg daily), α-methyldopa (doses of 750–1,500 mg daily) and placebo. The Duncan's Multiple Range Comparison test of the response scores for the 3 medications (the mean response scores for α-methyldopa, reserpine, and placebo groups were 1.7, 1.5, and 0.6, respectively) showed that α-methyldopa and reserpine equally improved the symptomatology of TD compared to placebo. This study had moderate risk of bias according to the Cochrane risk of

**Figure 4. Measured Efficacy of Pharmacologic Agents for Tardive Dyskinesia in Randomized, Placebo-Controlled Trials[a]**




| Agent | Effect Size (95% CI) | *P* Value | No. of Studies | No. of Subjects | $I^2$ |
|---|---|---|---|---|---|
| **Vitamin E** | | | | | 58 |
| | 0.31 (0.16 to 0.46) | <.001 | 15 | 502 | |
| **Vitamin $B_6$** | | | | | 0 |
| | 1.41 (0.98 to 1.85) | <.001 | 2 | 51 | |
| **VMAT2 Inhibitors** | | | | | 43.58 |
| Deutetrabenazine | 0.40 (0.04 to 0.77) | .03 | 1 | 117 | |
| Valbenazine | 0.72 (0.44 to 0.99) | <.001 | 1 | 225 | |
| Tetrabenazine | 3.23 (1.12 to 5.33) | .002 | 1 | 4 | |
| **Amantadine** | | | | | 0 |
| | 0.46 (0.05 to 0.87) | .03 | 3 | 47 | |
| **Calcium Channel Blockers** | | | | | 90.42 |
| Nifedipine | 4.38 (1.83 to 6.94) | <.001 | 1 | 4 | |
| Diltiazem | 0.03 (−0.13 to 2.57) | .94 | 1 | 17 | |
| **Other Agents** | | | | | |
| α-Methyldopa | 0.07 (−0.81 to 0.95) | .88 | 1 | 20 | |
| Biperiden | 0.91 (−0.07 to 1.88) | .07 | 1 | 18 | |
| Ceruletide | 1.10 (0.34 to 1.86) | <.001 | 1 | 66 | |
| Clonazepam | 0.65 (−0.01 to 1.30) | .05 | 1 | 19 | |
| Conjugated estrogens | 1.22 (−0.13 to 2.57) | .08 | 1 | 10 | |
| Ethyl-EPA | 0.01 (−0.44 to 0.45) | .98 | 1 | 77 | |
| Galantamine | 0.13 (−0.34 to 0.59) | .6 | 1 | 32 | |
| *Ginkgo biloba* | 0.73 (0.41 to 1.06) | <.001 | 1 | 157 | |
| Insulin | 1.27 (0.31 to 2.23) | .01 | 1 | 20 | |
| Levetiracetam | 0.96 (0.38 to 1.55) | <.001 | 1 | 50 | |
| Melatonin | 1.07 (0.44 to 1.70) | <.001 | 1 | 22 | |
| Naltrexone | 0.18 (−0.40 to 0.76) | .52 | 1 | 21 | |
| Piracetam | 0.64 (0.13 to 1.15) | .01 | 1 | 31 | |
| Reserpine | 0.07 (−0.81 to 0.95) | .88 | 1 | 30 | |
| Selegiline | 0.73 (0.03 to 1.44) | .04 | 1 | 28 | |
| Sulpiride | 0.77 (0.19 to 1.35) | .01 | 1 | 15 | |

[a]This figure depicts the summary effects of all pharmacologic agents that have been used to treat tardive dyskinesia in randomized, placebo-controlled trials.
Abbreviations: EPA = ethyl-eicosapentaenoic acid, VMAT2 = vesicular monoamine transporter 2.

bias tool: incomplete outcome data were not addressed, and random sequence generation and allocation concealment were unclear.

***Sulpiride.*** Sulpiride was investigated in a single blind, crossover, placebo-controlled study in 15 subjects.[65] It was found that 600 mg/d of sulpiride treatment led to significantly lower TD scores ($P<.01$) than placebo treatment.[65] This study had a low Jadad score of 2 and a high risk of bias according to the Cochrane risk of bias tool as only the participants were blinded and randomization procedure was unclear.

***Conjugated estrogens.*** Previous animal studies and hormonal studies in female schizophrenia patients suggest estrogen has different effects on dopamine dynamics in the mesolimbic and mesostriatal pathways.[87,88] A randomized, placebo-controlled, double-group study[57] tested the effect of estrogen replacement therapy in TD in a limited sample of 10 post-menopausal women. After 3 weeks of treatment, AIMS score decreased by 38% in the estrogen group and by 9% in the placebo group and did not reach statistical significance. This study was associated with a moderate risk of bias as randomization; allocation concealment was unclear, the small sample size and the imbalance between groups in baseline AIMS scores are other limitations of this trial.

***Ethyl-EPA.*** Impaired phospholipid metabolism in schizophrenia has been proposed, thus omega-3 fatty acids, EPA in particular, may have an effect on this impairment and improve the TD symptoms in this population.[56,89] Ethyl-EPA was evaluated in a 12-week, double-blind, randomized study[56] of ethyl-EPA 2 g/d versus placebo as supplemental medication in 77 subjects. Response rates

(≥ 30% improvement in TD symptoms) also did not differ significantly between EPA-treated subjects (45%) and placebo-treated subjects (32%) ($P = .6$). This study was of good methodological quality with the highest possible Jadad score of 5 and low risk of bias as per the Cochrane risk of bias tool.

***Galantamine.*** Chronic dopamine blockade due to antipsychotic use causes excitotoxicity and neurodegeneration of cholinergic neurons in rats. Therefore, it has been proposed that cholinesterase inhibitors such as galantamine may compensate for the loss of cholinergic neurons and improve TD by enhancing synaptic cholinergic activity.[55,56,90] A 30-week randomized, double-blind, placebo-controlled crossover trial of galantamine (8–24 mg) was conducted in 35 male patients with TD.[55] Galantamine reduced mean total Abnormal Involuntary Movement Scale (AIMS) scores more than placebo, but this difference was not statistically significant. This study had low risk of bias; however, authors did not provide enough information on random sequence generation and allocation concealment.

***Naltrexone and clonazepam.*** Based on the known role of striatopallidal enkephalinergic neurons in basal ganglia function, investigators have hypothesized a therapeutic potential for enkephalinergic opiate antagonism by naltrexone. Colocalization of γ-aminobutyric acid (GABA) and enkephalin in the basal ganglia suggests that a low dose of a GABA agonist, a benzodiazepine such as clonazepam, may augment the effects of naltrexone in hyperkinetic movement disorders.[59,91] In 2 double-blind, placebo-controlled, randomized, crossover trials,[59] effects of naltrexone (200 mg/d) alone (n = 9) and naltrexone in combination with clonazepam (0.25 to 0.5 mg; n = 14) were tested on TD. There were no significant effects of naltrexone alone (mean ± SD decrease in TD score, 0.1 ± 4.8) or low dose of clonazepam on TD, but the addition of naltrexone to clonazepam significantly improved TD (mean ± SD decrease in TD score, 4.0 ± 3.6). This study had moderate risk of bias due inadequate information on randomization process and blinding of outcome assessment.

A 12-week double-blind, placebo-controlled, crossover study[70] in 19 patients with TD revealed that 4.5 mg/d of clonazepam treatment alone reduced dyskinesia scores by 37.1% in the patient group overall, an effect that was reversed during placebo administration. This study had low risk of bias; however, authors did not provide enough information on random sequence generation and allocation concealment.

***Selegiline.*** Selegiline may improve TD symptoms due to its powerful antioxidant properties as established by increased levels of the antioxidant enzyme superoxide dismutase in rat striatum after selegiline use and reduction of oxidative stress by selegiline in rats that were treated with haloperidol.[92,93] Twenty-eight patients with TD were randomly assigned to selegiline (10 mg/d) or placebo groups for a period of 6 weeks.[58] A clinically significant improvement in the total AIMS score, defined as an improvement of 50% or greater, was observed in 5 patients (31%) receiving placebo and only 1 patient (8%) receiving selegiline. This study had moderate risk of bias; random sequence generation and allocation concealment were unclear.

## DISCUSSION

This systematic review showed that several agents have demonstrated efficacy compared to placebo and are very likely effective in the treatment of TD. VMAT2 inhibitors, vitamin E, vitamin $B_6$, and amantadine have demonstrated benefit compared to placebo in multiple controlled trials. The trials of the VMAT2 inhibitors appear to demonstrate a substantial benefit compared to placebo in single, well-conducted randomized controlled trials and appear to have a medium-to-large treatment effect when compared to placebo. Vitamin E is by far the most studied agent in treating TD and demonstrated a modest benefit compared to placebo. However, there was strong evidence of publication bias within the vitamin E trials. Also present was a negative association between the measured efficacy of vitamin E and the dose and duration of treatment. These findings suggest that even the modest benefit of vitamin E in the published literature may be overstated. Two vitamin $B_6$ trials suggested a large treatment benefit compared to placebo, but these were single site studies conducted by the same group. Additional trials are needed to replicate the initial positive findings with regard to vitamin $B_6$.

Vitamin E is the most studied agent in randomized, controlled trials on the treatment of TD. It may improve TD symptoms due to its antioxidant properties.[94] In randomized trials, vitamin E was associated with a medium-to-large treatment benefit when compared to placebo. However, several factors suggest the benefits of vitamin E for TD may be overstated. Firstly, most of the studies with vitamin E were of poor quality, with 8 trials having a Jadad score of 3 or less. This meta-analysis also found considerable publication bias, suggesting that the efficacy finding on vitamin E in TD may be overstated in the literature. Additionally, there was a significant negative association between measured efficacy of vitamin E and the dosage and duration of use.

Vitamin $B_6$ may improve TD as a free radical scavenger, similar to vitamin E.[95] Vitamin $B_6$ serves as a cofactor in the enzymatic decarboxylation of dopa to dopamine and other metabolic transformations including γ-aminobutyric acid and serotonin.[96,97] Two double-blind, randomized trials[41,42] on vitamin $B_6$ were conducted by the same research group, demonstrated a large benefit of this compound compared to placebo. The first study was associated with a high risk of bias, and the second study had low risk of bias according to the Cochrane risk of bias tool. The articles failed to provide the details regarding randomization, and it was unclear if blinding was maintained during outcome assessment in one of the studies.[42] Further replication of these initial promising trials is needed.

Strong evidence exists for the efficacy of VMAT2 inhibitors, valbenazine and deutetrabenazine, as these agents demonstrated moderate effect size. The 2 trials[40,43] on VMAT2 inhibitors were of high quality (Jadad score = 5).

The trial on valbenazine also suggested that it may have dose-related effects on efficacy.[40] Although the number of trials investigating these medications is low, the trials include large study samples and are of higher quality compared to other studies examining TD. Open label and non–placebo controlled trials on tetrabenazine and the RCT included in this meta-analysis support the efficacy of this medication class in TD.[69,98] VMAT2 inhibitors are hypothesized to improve TD by decreasing dopamine output.

TD is hypothesized to result from the up-regulation and sensitization of $D_2$ receptors after prolonged blockade by antidopaminergic medications.[17] This supersensitive state in the striatum may result in abnormal involuntary hyperkinetic movements. This hypothesis is supported by the clinical observation that increasing dopaminergic blockade can suppress TD temporarily.[99] Decreasing dopamine output may be a way to therapeutically target this mechanism and decrease abnormal motor movements. This decreased output can be achieved by the vesicular monoamine transporter type 2 inhibitors, which can reduce dopamine storage in vesicles and its release, which in turn curtails the hypothetical overstimulation of supersensitive $D_2$ dopamine receptors in the striatum.[100]

Three randomized, controlled trials[66,72,73] with a 2-week treatment duration, examined different doses of amantadine (maximum daily doses of 100 mg, 200 mg, and 300 mg) in TD treatment. This meta-analysis revealed that the standard mean difference of improvement with amantadine compared to placebo was statistically significant. All 3 amantadine studies had moderate risk of bias due to vaguely described randomization and blinding processes. It is unclear how anticholinergic drugs may improve TD symptoms. Contrary to the proposed treatment of TD, most studies in the literature have attempted to demonstrate an association between anticholinergic drug use and an increase in the incidence of TD. However, animal studies so far have not revealed an association between anticholinergic use and dopamine supersentivity.[101]

There are several limitations present in our meta-analysis. For all agents and medication classes other than vitamin E, there were very few trials available. The limited number of trials prevented us from investigating publication bias, heterogeneity, or moderators of treatment effect in these medications. Analysis of the vitamin E trials suggested that there may be significant issues with publication bias and heterogeneity in the literature.

A review of the clinical trials in TD reveals different levels of evidence for the medications that were found to improve TD symptoms in this meta-analysis and systematic review, which we now present in a hierarchical order: Strong evidence exists for the VMAT2 inhibitors valbenazine and deutetrabenazine, which were found to improve TD symptoms in double-blind, appropriately powered and randomized, placebo-controlled trials. There is moderate evidence from a single, double-blind RCT each for both *Ginkgo biloba* and clonazepam in the treatment of TD. Conflicting results from RCTs reveal weak evidence for the use of vitamin E in TD treatment. Evidence of publication bias and a significant negative association of dose and duration of treatment with measured efficacy also suggest that the benefits of vitamin E in TD may be overstated in the published literature. Weak evidence exists for amantadine from RCTs, with small sample sizes and considerable risk of bias as per the Cochrane risk of bias tool, which reported TD improvement with amantadine when used conjointly with neuroleptics. There is insufficient evidence for the efficacy of vitamin $B_6$ from 2 RCTs from the same group with limited sample size and significant risk of bias. There is insufficient evidence for several compounds that were examined in a single, double-blind RCT each such as levetiracetam, melatonin, piracetam, and reserpine. Positive efficacy outcomes were reported for following medications that were also examined in a single study each, albeit with smaller sample size and/or higher risk of bias: sulpiride, ceruletide, insulin, biperiden, conjugated estrogens, and α-methyldopa.

The American Academy of Neurology (AAN) published a guideline in 2013[102] that reported moderate evidence for *Ginkgo biloba* and clonazepam and weak evidence for amantadine and dopamine depleters and insufficient evidence for the use of vitamin E and vitamin $B_6$ for the treatment of tardive syndromes. Recommendations regarding the use of dopamine depleters should be reconsidered in light of the more recent RCT findings on valbenazine and deutetrabenazine. Findings on amantadine, *Ginkgo biloba*, and clonazepam have not received further investigation, and replication studies with rigorous scientific methodology are needed. Botulinum toxin and deep brain stimulation, which improved TD symptoms in case reports and uncontrolled studies, were found to have insufficient evidence as per the AAN guideline. They have not since been examined in controlled, randomized trials. The guideline reports insufficient evidence for vitamin E and vitamin $B_6$. Large head-to-head placebo-controlled trials between FDA-approved agents for TD and vitamin E and vitamin $B_6$ would be useful in determining the most efficacious and most cost-effective treatments for TD. Melatonin, piracetam, levetiracetam, and reserpine, which have shown benefit in higher-quality, decently powered individual studies and have a plausible biologic rationale, probably deserve further examination in larger, placebo-controlled clinical trials.

***Submitted:*** February 22, 2019; accepted December 16, 2019.

***Published online:*** May 26, 2020.

***Potential conflicts of interest:*** **Dr Bloch** is on the Scientific Advisory Board of Therapix Biosciences and has received research support from Biohaven Pharmaceuticals, Therapix Biosciences, Janssen Pharmaceuticals, and Neurocrine Biosciences and has received research support from the National Institutes of Health, the Tourette Association of America, the Brain and Behavior Research Foundation (formerly NARSAD), and the Patterson Foundation. **Drs Artukoglu** and **Szejko** and **Mr Li** have no conflicts of interest to disclose.

***Funding/support:*** No direct funding was provided for this research.

***Acknowledgments:*** The authors would like to thank Joshua Smith, MD; Jessica Levine, BA; Madeeha Nasir, MD; and Adam Lombroso, BA, for their careful review and critiques of this manuscript prior to submission. These individuals are affiliated with the Yale Child Study Center and have no conflicts of interest to disclose.

## REFERENCES


1. Leucht S, Corves C, Arbter D, et al. *Lancet*. 2009;373(9657):31–41.
2. Leucht S, Cipriani A, Spineli L, et al. *Lancet*. 2013;382(9896):951–962.
3. Miura T, Noma H, Furukawa TA, et al. *Lancet Psychiatry*. 2014;1(5):351–359.
4. Bandelow B, Chouinard G, Bobes J, et al. *Int J Neuropsychopharmacol*. 2010;13(3):305–320.
5. Depping AM, Komossa K, Kissling W, et al. *Cochrane Database Syst Rev*. 2010;(12):CD008120.
6. Durgam S, Earley W, Guo H, et al. *J Clin Psychiatry*. 2016;77(3):371–378.
7. Fornaro M, Stubbs B, De Berardis D, et al. *Int J Mol Sci*. 2016;17(2):241.
8. Lenze EJ, Mulsant BH, Blumberger DM, et al. *Lancet*. 2015;386(10011):2404–2412.
9. McIntyre RS, Gorwood P, Thase ME, et al. *J Clin Psychopharmacol*. 2015;35(6):706–710.
10. Thase ME, Youakim JM, Skuban A, et al. *J Clin Psychiatry*. 2015;76(9):1224–1231.
11. Arnold LE, Gadow KD, Farmer CA, et al. *J Child Adolesc Psychopharmacol*. 2015;25(3):203–212.
12. Greenaway M, Elbe D. *J Can Acad Child Adolesc Psychiatry*. 2009;18(3):250–260.
13. Stephens RJ, Bassel C, Sandor P. *J Child Adolesc Psychopharmacol*. 2004;14(2):255–266.
14. Moore TJ, Mattison DR. *JAMA Intern Med*. 2017;177(2):274–275.
15. Caroff SN, Campbell EC. *Psychiatr Clin North Am*. 2016;39(3):391–411.
16. Miyamoto S, Duncan GE, Marx CE, et al. *Mol Psychiatry*. 2005;10(1):79–104.
17. Waln O, Jankovic J. *Tremor Other Hyperkinet Mov (N Y)*. 2013;3:tre-03-161-4138-1.
18. Lieberman JA, Saltz BL, Johns CA, et al. *Br J Psychiatry*. 1991;158(4):503–510.
19. Chong SA, Tay JA, Subramaniam M, et al. *J Clin Psychopharmacol*. 2009;29(1):5–8.
20. Ascher-Svanum H, Zhu B, Faries D, et al. *J Clin Psychiatry*. 2008;69(10):1580–1588.
21. Kelly DL, Weiner E, Ball MP, et al. *J Psychopharmacol*. 2009;23(4):436–441.
22. Correll CU, Leucht S, Kane JM. *Am J Psychiatry*. 2004;161(3):414–425.
23. Pinninti NR, Faden J, Adityanjee A. *Clin Neuropharmacol*. 2015;38(5):183–197.
24. Arvanitis LA, Miller BG. *Biol Psychiatry*. 1997;42(4):233–246.
25. Tollefson GD, Beasley CM Jr, Tran PV, et al. *Am J Psychiatry*. 1997;154(4):457–465.
26. Jeste DV, Wyatt RJ. *Arch Gen Psychiatry*. 1982;39(7):803–816.
27. Egan MF, Apud J, Wyatt RJ. *Schizophr Bull*. 1997;23(4):583–609.
28. Soares KV, McGrath JJ. *Schizophr Res*. 1999;39(1):1–16, discussion 17–18.
29. Glazer WM, Morgenstern H, Schooler N, et al. *Br J Psychiatry*. 1990;157(4):585–592.
30. Caroff SN, Mann SC, Campbell EC, et al. *J Clin Psychiatry*. 2002;63(suppl 4):12–19.
31. Tarsy D, Baldessarini RJ, Tarazi FI. *CNS Drugs*. 2002;16(1):23–45.
32. Valbenazine [package insert]. San Diego, CA: Neurocrine Biosciences, Inc; July 2019.
33. Deutetrabenazine [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc; July 2019.
34. Chouinard G, Ross-Chouinard A, Annable L, Jones B. Extrapyramidal Symptom Rating Scale [ESRS]. In: *Rating Scales in Mental Health*. Hudson, OH: Lexi-Comp; 1980; 209–213.
35. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Revised Edition. Washington, DC: US Department of Health, Education, and Welfare; 1976.
36. Jadad AR, Moore RA, Carroll D, et al. *Control Clin Trials*. 1996;17(1):1–12.
37. Higgins J. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). Chichester, UK: The Cochrane Collaboration; 2011.
38. Comprehensive Meta-Analysis [computer program]. Englewood, NJ: Biostat, Inc; 2006.
39. Lohr JB, Cadet JL, Lohr MA, et al. *Schizophr Bull*. 1988;14(2):291–296.
40. Hauser RA, Factor SA, Marder SR, et al. *Am J Psychiatry*. 2017;174(5):476–484.
41. Lerner V, Miodownik C, Kaptsan A, et al. *J Clin Psychiatry*. 2007;68(11):1648–1654.
42. Lerner V, Miodownik C, Kaptsan A, et al. *Am J Psychiatry*. 2001;158(9):1511–1514.
43. Fernandez HH, Factor SA, Hauser RA, et al. *Neurology*. 2017;88(21):2003–2010.
44. Adler LA, Peselow E, Rotrosen J, et al. *Am J Psychiatry*. 1993;150(9):1405–1407.
45. Adler LA, Rotrosen J, Edson R, et al. *Arch Gen Psychiatry*. 1999;56(9):836–841.
46. Akhtar S, Jajor TR, Kumar S. *J Postgrad Med*. 1993;39(3):124–126.
47. Dabiri LM, Pasta D, Darby JK, et al. *Am J Psychiatry*. 1994;151(6):925–926.
48. Egan MF, Hyde TM, Albers GW, et al. *Am J Psychiatry*. 1992;149(6):773–777.
49. Elkashef AM, Ruskin PE, Bacher N, et al. *Am J Psychiatry*. 1990;147(4):505–506.
50. Lam LC, Chiu HF, Hung SF. *J Nerv Ment Dis*. 1994;182(2):113–114.
51. Shriqui CL, Bradwejn J, Annable L, et al. *Am J Psychiatry*. 1992;149(3):391–393.
52. Schmidt M, Meister P, Baumann P. *Eur Psychiatry*. 1991;6(4):201–207.
53. Adler LA, Edson R, Lavori P, et al. *Biol Psychiatry*. 1998;43(12):868–872.
54. Lohr JB, Caligiuri MP. *J Clin Psychiatry*. 1996;57(4):167–173.
55. Caroff SN, Walker P, Campbell C, et al. *J Clin Psychiatry*. 2007;68(3):410–415.
56. Emsley R, Niehaus DJ, Koen L, et al. *Schizophr Res*. 2006;84(1):112–120.
57. Glazer WM, Naftolin F, Morgenstern H, et al. *Psychoneuroendocrinology*. 1985;10(3):345–350.
58. Goff DC, Renshaw PF, Sarid-Segal O, et al. *Biol Psychiatry*. 1993;33(10):700–706.
59. Wonodi I, Adami H, Sherr J, et al. *J Clin Psychopharmacol*. 2004;24(4):441–445.
60. Huang CC, Wang RI, Hasegawa A, et al. *Psychopharmacology (Berl)*. 1981;73(4):359–362.
61. Kojima T, Yamauchi T, Miyasaka M, et al. *Psychiatry Res*. 1992;43(2):129–136.
62. Libov I, Miodownik C, Bersudsky Y, et al. *J Clin Psychiatry*. 2007;68(7):1031–1037.
63. Mouret J, Khomais M, Lemoine P, et al. *Eur Neurol*. 1991;31(4):199–203.
64. Shamir E, Barak Y, Shalman I, et al. *Arch Gen Psychiatry*. 2001;58(11):1049–1052.
65. Schwartz M, Moguillansky L, Lanyi G, et al. *J Neurol Neurosurg Psychiatry*. 1990;53(9):800–802.
66. Silver H, Geraisy N, Schwartz M. *J Clin Psychiatry*. 1995;56(4):167–170.
67. Suddath RL, Straw GM, Freed WJ, et al. *Pharmacol Biochem Behav*. 1991;39(3):743–745.
68. Bridler R. [article in German]. *Praxis (Bern 1994)*. 2001;90(18):809–810.
69. Jankovic J. *Ann Neurol*. 1982;11(1):41–47.
70. Thaker GK, Nguyen JA, Strauss ME, et al. *Am J Psychiatry*. 1990;147(4):445–451.
71. Zhang WF, Tan YL, Zhang XY, et al. *J Clin Psychiatry*. 2011;72(5):615–621.
72. Pappa S, Tsouli S, Apostolou G, et al. *Clin Neuropharmacol*. 2010;33(6):271–275.
73. Angus S, Sugars J, Boltezar R, et al. *J Clin Psychopharmacol*. 1997;17(2):88–91.
74. Woods SW, Saksa JR, Baker CB, et al. *J Clin Psychiatry*. 2008;69(4):546–554.
75. Loonen AJ, Verwey HA, Roels PR, et al. *J Clin Psychopharmacol*. 1992;12(1):39–42.
76. Greenberg DA. *Ann Neurol*. 1987;21(4):317–330.
77. Grebb JA, Ellsworth KA, Freed WJ. *Pharmacol Biochem Behav*. 1985;23(4):613–618.
78. Lynch BA, Lambeng N, Nocka K, et al. *Proc Natl Acad Sci U S A*. 2004;101(26):9861–9866.
79. Zisapel N, Egozi Y, Laudon M. *Brain Res*. 1982;246(1):161–163.
80. Escames G, Acuña Castroviejo D, Vives F. *Neuroreport*. 1996;7(2):597–600.
81. Pepeu G, Spignoli G. *Prog Neuropsychopharmacol Biol Psychiatry*. 1989;13(suppl):S77–S88.
82. Horvath B, Marton Z, Halmosi R, et al. *Clin Neuropharmacol*. 2002;25(1):37–42.
83. Miller R, Chouinard G. *Biol Psychiatry*. 1993;34(10):713–738.
84. Matsumoto T, Nakahara T, Uchimura H, et al. *Brain Res*. 1984;324(1):195–199.
85. Sourkes TL, Murphy GF, Chavez B, et al. *J Neurochem*. 1961;8(2):109–115.
86. Carlsson A. *Psychotropic Drugs*. 1957;6:363–372.
87. Thompson KN, Kulkarni J, Sergejew AA. *Acta Psychiatr Scand*. 2000;101(2):130–134.
88. Di Paolo T, Poyet P, Labrie F. *Eur J Pharmacol*. 1981;73(1):105–106.
89. Horrobin DF. *Schizophr Res*. 1998;30(3):193–208.
90. Mahadik SP, Laev H, Korenovsky A, et al. *Biol Psychiatry*. 1988;24(2):199–217.
91. Iakimovskiĭ AF, Bobrova IV. [article in Russian]. *Patol Fiziol Eksp Ter*. 1991;(6):20–22.
92. Knoll J. *Acta Neurol Scand suppl*. 1989;126:83–91.
93. Cohen G, Spina MB. *Ann Neurol*. 1989;26(5):689–690.
94. Jiang Q. *Free Radic Biol Med*. 2014;72:76–90.
95. Wondrak GT, Jacobson EL. *Subcell Biochem*. 2012;56:291–300.
96. Goodman LS. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. New York, NY: McGraw-Hill; 1996.
97. Dreyfus P. Vitamin and nutritional deficiencies. In: Seigel GJ, Alberts RW, Agranoff BW, et al, eds. *Basic Neurochemistry*. 1981;661–679.
98. Caroff SN, Aggarwal S, Yonan C. *J Comp Eff Res*. 2018;7(2):135–148.
99. Citrome L. *Expert Rev Neurother*. 2018;18(4):323–332.
100. Stahl SM. *CNS Spectr*. 2018;23(1):1–6.
101. Gardos G, Cole JO. *Am J Psychiatry*. 1983;140(2):200–202.
102. Bhidayasiri R, Fahn S, Weiner WJ, et al; American Academy of Neurology. *Neurology*. 2013;81(5):463–469.