Evidence-based guideline: Treatment of tardive syndromes: Report of the Guideline Development Subcommittee of the American Academy of Neurology

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SPECIAL ARTICLE

Evidence-based guideline: Treatment of tardive syndromes

Report of the Guideline Development Subcommittee of the American Academy of Neurology

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ABSTRACT

Objective: To make evidence-based recommendations regarding management of tardive syndromes (TDS), including tardive dyskinesias (TDD), by addressing 5 questions: 1) Is withdrawal of dopamine receptor blocking agents (DRBAs) an effective TDS treatment? 2) Does switching from typical to atypical DRBAs reduce TDS symptoms? 3) What is the efficacy of pharmacologic agents in treating TDS? 4) Do patients with TDS benefit from chemodenervation with botulinum toxin? 5) Do patients with TDS benefit from surgical therapy?

Methods: PsycINFO, Ovid MEDLINE, EMBASE, Web of Science, and Cochrane were searched (1966–2011). Articles were classified according to a 4-tiered evidence-rating scheme; recommendations were tied to the evidence.

Results and recommendations: Clonazepam probably improves TDD and ginkgo biloba probably improves TDS (both Level B); both should be considered as treatment. Risperidone may improve TDS but cannot be recommended as treatment because neuroleptics may cause TDS despite masking symptoms. Amantadine and tetrabenazine might be considered as TDS treatment (Level C). Diltiazem should not be considered as TDD treatment (Level B); galantamine and eicosapentaenoic acid may not be considered as treatment (Level C). Data are insufficient to support or refute use of acetazolamide, bromocriptine, thiamine, baclofen, vitamin E, vitamin B_6, selegiline, clozapine, olanzapine, melatonin, nifedipine, fluperlapine, sulpiride, flupenthixol, thiopropazate, haloperidol, levetiracetam, quetiapine, ziprasidone, sertindole, aripiprazole, buspirone, yi-gan san, biperiden discontinuation, botulinum toxin type A, electroconvulsive therapy, α-methyldopa, reserpine, and pallidal deep brain stimulation as TDS treatments (Level U). Data are insufficient to support or refute TDS treatment by withdrawing causative agents or switching from typical to atypical DRBA (Level U). ***Neurology*® 2013;81:463–469**

GLOSSARY

AAN = American Academy of Neurology; **AIMS** = Abnormal Involuntary Movement Scale; **BoNT** = botulinum toxin; **DBS** = deep brain stimulation; **DRBA** = dopamine receptor blocking agent; **EPA** = eicosapentaenoic acid; **GABA** = γ-aminobutyric acid; **RCT** = randomized controlled trial; **TBZ** = tetrabenazine; **TD** = tardive dystonia; **TDD** = tardive dyskinesia; **TDS** = tardive syndrome.

Tardive syndromes (TDS) are disorders that fulfill the following criteria: history of at least 3 months' total cumulative neuroleptic exposure during which the exposure can be continuous or discontinuous, presence of at least "moderate" abnormal involuntary movements in one or more body areas or at least "mild" movements in 2 or more body areas, and absence of other conditions that might produce abnormal involuntary movements.[1] Various involuntary movements, including lingual-facial-buccal movements, are recognized as tardive dyskinesia (TDD) symptoms. TDS includes not only lingual-facial-buccal dyskinesia but also the variant forms, collectively termed *tardive syndromes*.[2–8] In this guideline, *tardive dyskinesia* encompasses all forms of persistent dyskinesia caused by dopamine receptor blocking agents (DRBAs).

TDS prevalence is estimated to be 30% in outpatients with schizophrenia treated with neuroleptics.[9–11] TDS

Supplemental data at www.neurology.org

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develops at approximately a 5% rate yearly, with a cumulative 5-year incidence of approximately 20% to 25%.[12,13]

This guideline addresses 5 questions regarding medical and surgical treatments for TDS management:

1. Is withdrawal of DRBAs an effective TDS treatment?
2. Does switching from typical to atypical DRBAs reduce TDS symptoms?
3. What is the efficacy of pharmacologic agents in treating TDS?
4. Do patients with TDS benefit from chemodenervation with botulinum toxin (BoNT)?
5. Do patients with TDS benefit from surgical therapy?

DESCRIPTION OF THE ANALYTIC PROCESS The American Academy of Neurology (AAN) empaneled an expert group to develop the guideline (appendices e-1 and e-2 on the *Neurology*® Web site at www.neurology.org). PsycINFO, Ovid MEDLINE, EMBASE, Web of Science, and Cochrane were searched (1966–2011) (appendices e-3–e-7). The search was supplemented using the bibliography of retrieved articles and panelists' knowledge and following the AAN's process manual.[14] We included studies of the following TDS treatments: neuroleptic withdrawal, anticholinergics, benzodiazepines, β-blockers, calcium channel blockers, cholinergics, GABAergic compounds, neuroleptic medications (including dose reduction and cessation), non-neuroleptic compounds that affect the dopamine and noradrenaline systems, vitamin B_6, and vitamin E. The preferred outcome measures are objective clinical rating scales of TDS severity (e.g., Abnormal Involuntary Movement Scale [AIMS]).[15] Two panelists reviewed abstracts and titles for relevance and rated selected studies using the AAN therapeutic classification scheme (appendix e-8). Recommendations were linked to the evidence (appendix e-9). Disagreements regarding classification were resolved by consensus. See table e-1 for summary of the evidence.

ANALYSIS OF EVIDENCE **Is withdrawal of DRBAs an effective TDS treatment?** Limited evidence is available to determine the long-term effect of antipsychotic withdrawal on TDS. Different study designs and heterogeneous study populations examining DRBA withdrawal result in conflicting conclusions. One Class III study compared an anticholinergic challenge with a 10-week neuroleptic withdrawal in 36 patients with TDS. The neuroleptic withdrawal significantly increased dyskinesia and dysphoria, resulting in early therapy termination in 33% of patients and return to prior neuroleptics poststudy.[16] Another Class III study found no significant worsening of tardive dystonia (TD) or psychiatric relapse in patients with chronic schizophrenia randomized to placebo for 6 weeks or their regular injectable fluphenazine.[17] Short-term studies also suggest that TDS worsens during the first few weeks after neuroleptic withdrawal (Class III and IV studies).[18,19]

Conclusion and recommendation. Data are insufficient to support or refute TDS treatment by DRBA withdrawal (Level U).

Clinical context. The American Psychiatric Association Task Force recommends antipsychotic withdrawal only in patients who can tolerate it.[20] Despite limited evidence, clinical impression indicates that short-term withdrawal may worsen dyskinesias, whereas adding antipsychotics with stronger extrapyramidal symptoms can reduce TDS.[10] Psychotic relapse predictors include younger age, higher baseline antipsychotic dosage, and shorter hospitalization.[21]

Does switching from typical to atypical DRBAs reduce TDS symptoms? Atypical antipsychotics are believed to have a lower propensity to cause TDS than typical DRBAs,[22–25] suggesting that changing from typical to atypical DRBAs might reduce TDS symptoms. Current evidence is limited to Class IV studies[26–30] with conflicting results.[31–33]

Conclusion and recommendation. Data are insufficient to support or refute TDS treatment by changing to atypical antipsychotics (Level U, Class IV studies).

What is the efficacy of pharmacologic agents in treating TDS? ***Acetazolamide.*** One Class III study examined the effect of acetazolamide and thiamine coadministration on TDD.[34] Patients older than 73 years received acetazolamide 1.5 g/d in 3 divided doses whereas younger patients received acetazolamide 2 g/d together with thiamine 1.5 g.[34] AIMS scores decreased from baseline by 46% in older patients and 41% in younger patients (both groups: $p < 0.01$ relative to placebo).

Amantadine. Several controlled and uncontrolled studies examined the effect of amantadine on patients with TDS.[35–39] One Class II, 18-week, double-blind, crossover, randomized controlled trial (RCT) reported amantadine to be beneficial in TDS when used conjointly with neuroleptics.[35] Patients were treated with amantadine (300 mg/d) and either a neuroleptic alone or a neuroleptic and placebo for 7 weeks. Overall, dyskinesia was reduced by 15% as measured by the AIMS in patients taking amantadine ($p = 0.05$).

Conclusions. Acetazolamide and thiamine reduced TDS in one Class III study. Amantadine reduced TDS when used conjointly with a neuroleptic during the first 7 weeks (1 Class II study, 2 Class III studies).

Recommendations. Data are insufficient to support or refute TDS treatment with acetazolamide and thiamine (Level U). Amantadine with neuroleptics may be considered to treat TDS for short-term use (Level C).

Clinical context. Only flupentixol decanoate, chlorpromazine, haloperidol, trifluoperazine, and thioridazine were tested with amantadine in these studies.

The efficacy of amantadine plus other neuroleptics in TDS treatment is unknown. Because safety data are unavailable concerning long-term use of only typical neuroleptics as TDS suppressive agents and because of these agents' propensity to cause TDS, the evidence suggests only potential efficacy short-term.

First-generation antipsychotics. A Class II, 8-week study of hospitalized patients with chronic schizophrenia with TDS found no difference in dyskinesia ratings in patients taking haloperidol (20 mg) relative to placebo.[40] However, another Class II study evaluated haloperidol for 8 weeks and found a decreased AIMS score.[e1] In this study, haloperidol reduced TDS for only the first 2 weeks of treatment, after which TDS returned and caused an akinetic-rigid syndrome.[e1] Multiple Class III, single-center, double-masked, parallel-group studies using haloperidol, molindone, sulpiride, fluperlapine, and flupenthixol found no significant benefit for treating TDS.[31,e2–e5] Suppressive effects are pronounced (67% improvement) in short-term studies,[e1,e2,e4] but the therapeutic efficacy of long-term suppression (>8 weeks) is unclear. A Class III study evaluated individual use of haloperidol and thiopropazate relative to a baseline placebo period.[e6] After 4-week treatment relative to baseline, oral dyskinesia was reduced 74% ($p < 0.01$) with haloperidol use and 27% ($p < 0.05$) with thiopropazate use.

Conclusions. Haloperidol possibly reduces TDS movements for up to 2 weeks (2 Class II studies,[40,e1] 1 Class III study[e6]) but is associated with increased akinetic-rigid syndrome (1 Class II study[e7]). Data are insufficient to support or refute the use of thiopropazate in reducing oral dyskinesia (1 Class III study[e6]).

Recommendations. Data are insufficient to support or refute the use of thiopropazate, molindone, sulpiride, fluperlapine, and flupenthixol in treating TDS (Level U).

Clinical context. Although haloperidol and thiopropazate possibly reduce TDS, they are not recommended because of the competing risk of akinetic-rigid syndrome. Safety data are unavailable concerning long-term use of typical antipsychotics as TDS suppressive agents, and these drugs themselves can cause TDS; these significant risks outweigh the benefits of any short-term use of typical antipsychotics.

Second-generation antipsychotics: Clozapine, risperidone, olanzapine, and other agents. Atypical antipsychotics can be defined as compounds that effect an antipsychotic response with a lower affinity for inducing extrapyramidal symptoms.[e8] However, the amount of striatal D2 receptor occupancy is not uniform among the second-generation agents, and these agents tend to induce these adverse effects.

One Class III, single-blind, crossover study compared clozapine with haloperidol in patients with schizophrenia with TDS.[e7] Patients taking clozapine up to the maximum dose (225 mg/d) did not significantly improve. Another Class III study and several Class IV studies, however, found significant improvement with clozapine.[32,e6]

In a Class II, 8-week, multicenter, double-blind study of hospitalized patients with chronic schizophrenia with TDS, patients treated with risperidone (6–16 mg) had lower dyskinetic scores than those receiving placebo ($p < 0.05$).[33] Another Class II study evaluated the effect of risperidone in 49 patients with schizophrenia with severe TDD. Significant improvement in TDD in the risperidone group (6 mg/d) was noted after 8 weeks, mainly in the lingual-facial-buccal area ($p < 0.001$).[e9] One Class III, 24-week study compared the efficacy of risperidone and olanzapine in patients with schizophrenia with TDD.[e10] AIMS scores decreased significantly in both groups (risperidone: -7.4 ± 6.9, $p < 0.0001$; olanzapine: -6.2 ± 8.0, $p = 0.0002$). However, greater change occurred in the slope of AIMS scores in the risperidone group relative to that in the olanzapine group ($p = 0.0001$).

One 8-month, Class III study found that olanzapine reduced TDD.[e11] In this study, patients with TDD received a mean 12-mg/d dose; no placebo group was included. At the study's end, 70% of patients no longer met TDD criteria. Another Class III study[e10] evaluated olanzapine use to treat TDD. After the 24-week treatment period, the AIMS score had decreased by approximately 30% relative to baseline ($p = 0.0002$). A few Class IV studies also found TDD reduction with olanzapine.[e12–e14]

Other atypical antipsychotics, including quetiapine, ziprasidone, aripiprazole, and sertindole, may serve as TDD treatment alternatives. However, only Class IV case reports regarding these medications exist.

Conclusions. Data are conflicting regarding the use of clozapine (conflicting Class III studies). Risperidone (2 Class II studies, 1 Class III study) is probably effective in reducing TDD. Olanzapine is possibly effective in reducing TDD (2 Class III studies). The safety of risperidone and olanzapine as a TDS suppressant for use beyond 48 weeks has not been addressed.[e15]

There is no evidence to determine the efficacy of quetiapine, ziprasidone, aripiprazole, and sertindole in TDS treatment.

Recommendations. Because neuroleptic agents may themselves cause TDS and may mask its symptoms rather than treat it, these drugs cannot be recommended for TDS treatment (Level U). Caution is advised when using risperidone or olanzapine to reduce TDS.

Electroconvulsive therapy. Only case reports have documented TDD reduction with electroconvulsive therapy.

Conclusion and recommendation. Data are insufficient to determine the efficacy of electroconvulsive therapy for TDD treatment (Level U).

Dopamine-depleting agents: Tetrabenazine, reserpine, and α-methyldopa. One Class III study compared

haloperidol use with tetrabenazine (TBZ) use (100 mg/d for 14 weeks).[e3] Another Class III, nonrandomized, single-blind study compared TBZ efficacy using a randomized videotape protocol pre- and posttreatment.[e16] Subjects discontinued neuroleptics and other TDS treatments at least 30 days prestudy. Reductions were seen posttreatment (mean dose 57.9 mg/d) on both the patient AIMS self-rating (60.4%, $p < 0.001$) and the AIMS motor subset evaluated by the blinded videotape raters (54.2%, $p < 0.001$). TBZ was well tolerated, and all patients continued to take it poststudy. These results are supported by Class IV, long-term, observational studies.[e3,e17]

Another Class III study compared reserpine, α-methyldopa, and placebo. Reserpine (0.75–1.5 mg/d) and α-methyldopa (750–1,500 mg/d) individually produced significant TDS reduction relative to placebo.[e18]

Conclusions. TBZ possibly reduces TDS symptoms (2 consistent Class III studies). One study (Class III) found reserpine and α-methyldopa effective in treating TDS.

Recommendations. TBZ may be considered in treating TDS (Level C). Data are insufficient to determine the efficacy of reserpine or α-methyldopa in treating TDS (Level U).

Clinical context. TBZ reduces TDS symptoms; there is no evidence that long-term TBZ administration induces TDS, but it can cause parkinsonism.

Dopamine agonists. Bromocriptine was combined with neuroleptics to treat TDS in one Class III study and one Class IV study.[e19,e20] The former study was a double-blind RCT that evaluated bromocriptine use in patients with TDS. Patients not taking neuroleptics were treated with thioridazine concomitantly with bromocriptine, whereas others continued on neuroleptics at a constant dose.[e19] There was no significant TDS reduction with bromocriptine.

Conclusion and recommendation. Data are insufficient to support or refute the use of bromocriptine for TDS treatment (Level U).

Cholinergic drugs. Cholinergic drugs (including choline, lecithin, physostigmine, tacrine, donepezil, rivastigmine, deanol, meclofenoxate, and galantamine) have been tried in TDS treatment.

One Class II study of galantamine in 35 patients with schizophrenia and TDS found that galantamine did not lessen TDS,[e21] and there was evidence of increased parkinsonism.

Conclusion. Galantamine is possibly ineffective in treating TDS (1 Class II study).

Recommendations. Galantamine might not be considered in treating TDS (Level C). Data are insufficient to determine the effectiveness of other cholinergic drugs in treating TDS (Level U).

Anticholinergic drugs. No controlled trials examining the efficacy of benztropine, biperiden, chlorprothixene, and trihexyphenidyl in treating TDS were reported.

Conclusion and recommendation. Data are insufficient to determine the effectiveness of anticholinergic drugs in treating TDS (Level U).

Biperiden (Akineton) discontinuation. One Class III, double-blind, placebo-controlled study evaluated the withdrawal of biperiden in 10 patients with chronic schizophrenia and TDS, utilizing the AIMS as the primary outcome.[e22] A significant AIMS score reduction occurred in the oral region (lingual-facial-buccal syndrome) ($p < 0.001$) within 2 weeks. However, parkinsonism increased after discontinuation in several patients ($p < 0.05$).

Conclusion and recommendation. Data are insufficient to determine the effectiveness of biperiden discontinuation in treating TDS (Level U, 1 Class III study).

Antioxidants. One Class II, multicenter, placebo-controlled, parallel-group, double-blind study randomized 158 patients to receive either vitamin E 1,600 IU/d (n = 73) or placebo (n = 85) for 2 years.[e23] One hundred seven patients (70% active, 66% placebo) completed at least 1 year of treatment. No significant effects of vitamin E were observed on total AIMS scores or other dyskinesia outcome measures. Two other short-term (2-week) Class II studies and 1 Class III study involving older patients also failed to reveal a therapeutic effect.[e24–e26] However, other Class II and Class III studies found evidence of reduced TDS severity with doses ranging from 1,200 to 1,600 IU/d for 4 to 12 weeks.[e27–e32] Overall symptom reduction in the positive studies ranged from 18.5% to 43% as measured by the AIMS.[e27,e28,e30–e32] Three Class II studies suggested that the most pronounced effect of vitamin E occurred in patients with recent TDS onset (within 5 years).[e28,e31,e32]

Several other agents with antioxidant properties have been tried in TDS. Melatonin was evaluated in 2 Class II, double-blind, placebo-controlled, crossover studies.[e33,e34] The first study involved 19 patients with schizophrenia and TDS randomized to either 2 mg/d melatonin or placebo for 10 weeks.[e33] A single rater administered the AIMS and found no difference between melatonin and placebo (mean change in melatonin group = -0.89 ± 1.13; mean change in placebo group = -0.84 ± 1.38, $p = 0.91$). The second Class II study used a higher melatonin dose (10 mg/d) and longer treatment duration (16 weeks).[e34] In this study, 77% of subjects (n = 17) were reported to have greater AIMS score reductions during treatment with melatonin than with placebo ($p = 0.001$).

A Class III, 6-week, double-blind, placebo-controlled study examined the efficacy of selegiline in 33 patients with TDS.[e35] When baseline scores and sex were controlled, the group receiving selegiline had significantly less TDS reduction relative to the placebo group.

One 12-week, double-blind, Class II RCT compared eicosapentaenoic acid (EPA) and placebo in reducing TDS. Eighty-four patients with schizophrenia or schizoaffective disorder with established TDS were randomized to either ethyl-EPA 2 g/d or placebo.[e36] The difference between EPA-treated subjects (n = 17, 45%) and placebo-treated subjects (n = 12, 32%) (p = 0.6) was nonsignificant.

Another double-blind, Class I RCT compared ginkgo biloba extract (EGb-761) and placebo in inpatients with schizophrenia and TDS.[e37] Subjects were randomly assigned to 12-week treatment with either EGb-761 240 mg/d (n = 78) or placebo (n = 79). AIMS scores decreased in patients with TDS receiving EGb-761 treatment relative to scores for those receiving placebo (2.13 ± 1.75 vs −0.10 ± 1.69, $p < 0.0001$).

In a small Class III, double-blind, placebo-controlled, 4-week, crossover study, 15 patients with schizophrenia and schizoaffective disorder receiving vitamin B_6 (400 mg)[e38] reported greater reduction on the TDD subscale of the Extrapyramidal Symptom Rating Scale than those receiving placebo (mean 68.6%, SD 14.4% vs mean 32.8%, SD 57.0%).

Another Class III, nonrandomized, single-blind study used a randomized pre- and posttreatment videotape protocol to examine the efficacy of the traditional Japanese herbal medicine yi-gan san in 22 patients with schizophrenia with TDS.[e39] A significant AIMS total score reduction (56%) after a 12-week yi-gan san treatment (7.5 g/d) was observed ($p < 0.0001$), and no patients worsened.

Conclusions and recommendations. EGb-761 is probably useful in TDS treatment (1 Class I study), but data are limited to inpatients with schizophrenia (Level B).

Based on 4 Class II and numerous Class III studies, data are conflicting regarding vitamin E efficacy in treating TDS. Data are insufficient to determine the efficacy of vitamin E (Level U).

Based on 1 Class II study, EPA is possibly ineffective in treating TDS and might not be considered (Level C).

Melatonin is possibly ineffective in treating TDS at a 2-mg/d dose (1 Class II study) but is possibly effective in treating TDS at a 10-mg/d dose (1 Class II study). Evidence regarding TDS treatment with melatonin is conflicting (Level U).

Data are insufficient to support or refute the use of other antioxidants, including vitamin B_6, selegiline, and yi-gan san, in treating TDS (Level U).

GABA agonists. One Class I, 12-week, double-blind, crossover RCT using the Maryland Psychiatric Research Center Movement Disorder Scale tested the efficacy of clonazepam in 19 patients with TDD who were treated with neuroleptics.[e40] A reduction in dyskinesia ($p < 0.001$) and dystonic ($p < 0.001$) symptoms was noted. In 5 patients who continued clonazepam for up to 9 months as an open study, the drug's antidyskinetic effect was absent after 5 to 8 months of continuous treatment.

Baclofen, a $GABA_B$ agonist, was evaluated in several RCTs. In 2 Class II studies, baclofen given in conjunction with neuroleptic agents significantly reduced TDD.[e41,e42] However, another Class II study found no beneficial effects of baclofen use alone in TDD.[e43]

Conclusions and recommendations. Based on 1 Class I study, clonazepam is probably effective in decreasing TDD symptoms short-term (approximately 3 months) and should be considered for short-term TDD treatment (Level B). Data are insufficient to support or refute baclofen use in treating TDD (Level U).

Levetiracetam. Following several prospective open-label trials[e44,e45] and case reports[e46] suggesting levetiracetam efficacy in patients with TDD, 1 double-blind RCT reported significant TDD reduction after a 12-week treatment with levetiracetam up to 3,000 mg/d, but the dropout rate exceeded 20% (Class III).[e47]

Conclusion and recommendation. Data are insufficient to recommend levetiracetam as TDS treatment (Level U, 1 Class III study).

Calcium channel blockers. Limited evidence is available on the efficacy of calcium channel blockers in TDS. One Class I, double-blind, placebo-controlled study showed no improvement with diltiazem (diltiazem first [n = 8] vs placebo first [n = 9]).[e48] The negative results may be related to the study's short duration (3 weeks). A Class III study showed no improvement with a single oral dose relative to placebo in 6 subjects.[e49] One double-blind, crossover study reported significant TDS reduction after an 8-week treatment with nifedipine up to 90 mg/d, but the study lacked clear inclusion criteria and uniform patient baseline characteristics (Class IV).[e50]

Conclusions and recommendations. Data are insufficient to support or refute nifedipine use in treating TDD (Level U). Diltiazem probably does not reduce TDD and should not be considered as treatment (Level B, 1 Class I study).

Buspirone. Limited evidence is available on the efficacy of buspirone in TDD. One Class III study demonstrated significant improvement of AIMS scores with buspirone in dosages up to 180 mg/d over 12 weeks.[e51]

Conclusion and recommendation. Data are insufficient to support or refute buspirone use in treating TDD (Level U, 1 Class III study).

Do patients with TDS benefit from chemodenervation with BoNT? BoNT injection is currently considered the optimal treatment for focal dystonia. However, efficacy data for BoNT in TDS treatment derive from open-label, retrospective studies (Class IV).

Conclusion and recommendation. Data are insufficient to support or refute BoNT use to treat TDS symptoms (Level U).

Do patients with TDS benefit from surgical therapy? Stereotactic pallidotomy and pallidal deep brain stimulation (DBS) for treating dystonia has resurged.[e52,e53] Evidence related to pallidal DBS use in patients with TD is limited (Class IV studies comprising case reports or small case series).[e54–e58]

Conclusion and recommendation. Data are insufficient to support or refute pallidal DBS use in treating TDS (Class IV studies) (Level U).

RECOMMENDATIONS FOR FUTURE RESEARCH

Comparison of the various TDS interventions is difficult because different scales have been used to measure TDS, statistical techniques used to assess intervention efficacy have varied widely, and results reporting lacks uniformity.

Well-designed, double-masked RCTs with specific inclusion criteria are needed to determine which interventions are most effective for reducing TDS symptoms. Separate study of certain TDS forms may be necessary, because not all TDS are treated uniformly. Valid, reliable scales for measuring TDS are critically needed.

AUTHOR CONTRIBUTIONS

Roongroj Bhidayasiri: study concept or design, acquisition of data, drafting/revising the manuscript, analysis or interpretation of data, critical revision of the manuscript for important intellectual content, study supervision. Stanley Fahn and William J. Weiner: analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Gary S. Gronseth and Kelly L. Sullivan: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Theresa A. Zesiewicz: study concept or design, acquisition of data, drafting/revising the manuscript, analysis or interpretation of data, critical revision of the manuscript for important intellectual content, study supervision.

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DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. Formal practice recommendations are not intended to replace clinical judgment.

CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology*® peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

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REFERENCES

1. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. Arch Gen Psychiatry 1982;39:486–487.
2. Stacy M, Jankovic J. Tardive tremor. Mov Disord 1992;7:53–57.
3. Stacy M, Cardoso F, Jankovic J. Tardive stereotypy and other movement disorders in tardive dyskinesias. Neurology 1993;43:937–941.
4. Sachdev P. Tardive blepharospasm. Mov Disord 1998;13:947–951.
5. Fernandez HH, Friedman JH. Classification and treatment of tardive syndromes. Neurologist 2003;9:16–27.
6. Burke RE, Kang UJ, Jankovic J, Miller LG, Fahn S. Tardive akathisia: an analysis of clinical features and response to open therapeutic trials. Mov Disord 1989;4:157–175.
7. Burke RE, Fahn S, Jankovic J, et al. Tardive dystonia: late-onset and persistent dystonia caused by antipsychotic drugs. Neurology 1982;32:1335–1346.
8. Bharucha KJ, Sethi KD. Tardive tourettism after exposure to neuroleptic therapy. Mov Disord 1995;10:791–793.
9. Chouinard G, Annable L, Ross-Chouinard A, Mercier P. A 5-year prospective longitudinal study of tardive dyskinesia: factors predicting appearance of new cases. J Clin Psychopharmacol 1988;8:21S–26S.
10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.
11. Correll CU, Rummel-Kluge C, Corves C, et al. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomised controlled trials. Schizophr Bull 2009;35:443–457.
12. Morgenstern H, Glazer WM. Identifying risk factors for tardive dyskinesia among long-term outpatients maintained with neuroleptic medications: results of the Yale Tardive Dyskinesia Study. Arch Gen Psychiatry 1993;50:723–733.
13. Gardos G, Casey DE, Cole JO, et al. Ten-year outcome of tardive dyskinesia. Am J Psychiatry 1994;151:836–841.
14. Gronseth GS, Woodroffe LM, Getchius TS. Clinical Practice Guideline Process Manual. St. Paul, MN: American Academy of Neurology; 2011.
15. Guy W. Abnormal Involuntary Movement Scale. In: ECDEU Assessment Manual for Psychopharmacology. Washington, DC: US Government Printing Office; 1976:534–537.
16. Gardos G, Cole JO, Rapkin RM, et al. Anticholinergic challenge and neuroleptic withdrawal: changes in

dyskinesia and symptom measures. Arch Gen Psychiatry 1984;41:1030–1035.
17. Shenoy RS, Sadler AG, Goldberg SC, Hamer RM, Ross B. Effects of a six-week drug holiday on symptom status, relapse, and tardive dyskinesia in chronic schizophrenics. J Clin Psychopharmacol 1981;1:141–145.
18. Carpenter WT, Rey AG, Stephens JH. Covert dyskinesia in ambulatory schizophrenia. Lancet 1980;2:212–213.
19. Branchey MH, Branehey LB, Richardson MA. Effects of gradual decrease and discontinuation of neuroleptics on clinical condition and tardive dyskinesia [proceedings]. Psychopharmacol Bull 1981;17:118–120.
20. American Psychiatric Association. Tardive Dyskinesia: A Task Force Report of the American Psychiatric Association. Washington, DC: American Psychiatric Publishing; 1992.
21. Gilbert PL, Harris MJ, McAdams LA, Jeste DV. Neuroleptic withdrawal in schizophrenic patients: a review of the literature. Arch Gen Psychiatry 1995;52:173–188.
22. Kane JM. Tardive dyskinesia rates with atypical antipsychotics in adults: prevalence and incidence. J Clin Psychiatry 2004;65(suppl 9):16–20.
23. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry 2004; 161:414–425.
24. Barnes TR, McPhillips MA. Novel antipsychotics, extrapyramidal side effects and tardive dyskinesia. Int Clin Psychopharmacol 1998;13(suppl 3):S49–S57.
25. Kane JM. Tardive dyskinesia: epidemiological and clinical presentation. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: The Fourth Generation of Progress. New York: Raven Press; 1995:1485–1495.
26. Dalack GW, Becks L, Meador-Woodruff JH. Tardive dyskinesia, clozapine, and treatment response. Prog Neuropsychopharmacol Biol Psychiatry 1998;22:567–573.
27. Bassitt DP, Louza Neto MR. Clozapine efficacy in tardive dyskinesia in schizophrenic patients. Eur Arch Psychiatry Clin Neurosci 1998;248:209–211.
28. Modestin J, Stephan PK, Erni T, et al. Prevalence of extrapyramidal syndromes in psychiatric inpatients and the relationship of clozapine treatment to tardive dyskinesia. Schizophr Res 2000;42:223–230.
29. Soutullo CA, Keck PE Jr, McElroy SL. Olanzapine in the treatment of tardive dyskinesia: a report of two cases. J Clin Psychopharmacol 1999;19:100–101.
30. Vesely C, Kufferle B, Brucke T, Kasper S. Remission of severe tardive dyskinesia in a schizophrenic patient treated with the atypical antipsychotic substance quetiapine. Int Clin Psychopharmacol 2000;15:57–60.
31. Korsgaard S, Noring U, Gerlach J. Fluperlapine in tardive dyskinesia and parkinsonism. Psychopharmacology 1984; 84:76–79.
32. Simpson GM, Lee JH, Shrivastava RK. Clozapine in tardive dyskinesia. Psychopharmacology 1978;56:75–80.
33. Chouinard G. Effects of risperidone in tardive dyskinesia: an analysis of the Canadian multicenter risperidone study. J Clin Psychopharmacol 1995;15:36S–44S.
34. Cowen MA, Green M, Bertollo DN, Abbott K. A treatment for tardive dyskinesia and some other extrapyramidal symptoms. J Clin Psychopharmacol 1997;17: 190–193.
35. Angus S, Sugars J, Boltezar R, Koskewich S, Schneider NM. A controlled trial of amantadine hydrochloride and neuroleptics in the treatment of tardive dyskinesia. J Clin Psychopharmacol 1997;17:88–91.
36. Decker BL, Davis JM, Jonowsky DS, el-Yousef MK, Sekerke HJ. Amantadine hydrochloride treatment of tardive dyskinesia. N Engl J Med 1971;285:860.
37. Allen RM. Palliative treatment of tardive dyskinesia with combination of amantadine-neuroleptic administration. Biol Psychiatry 1982;17:719–727.
38. Freudenreich O, McEvoy JP. Added amantadine may diminish tardive dyskinesia in patients requiring continued neuroleptics. J Clin Psychiatry 1995;56:173.
39. Pappa S, Tsouli S, Apostolou G, Mavreas V, Konitsiotis S, et al. Effects of amantadine on tardive dyskinesia: a randomised double-blind placebo-controlled study. Clin Neuropharmacol 2010;33:271–275.
40. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993; 13:25–40.

CORRECTION

Evidence-based guideline: Treatment of tardive syndromes: Report of the Guideline Development Subcommittee of the American Academy of Neurology

In the evidence-based guideline "Treatment of tardive syndromes: Report of the Guideline Development Subcommittee of the American Academy of Neurology" by R. Bhidayasiri et al. (*Neurology*® 2013;81:463–469), there was an error in table e-1; the corrected version was posted with the article on September 4, 2013. In addition, 2 studies were inadvertently excluded from the literature search (and thus from the guideline). The following references should have been cited. The authors regret the errors.

1. Lerner V, Miodownik C, Kaptsan A, et al. Vitamin B6 treatment for tardive dyskinesia: a randomized, double-blind, placebo-controlled, crossover study. J Clin Psychiatry 2007;68:1648–1654.
2. Libov I, Miodownik C, Bersudsky Y, et al. Efficacy of piracetam in the treatment of tardive dyskinesia in schizophrenic patients: a randomized, double-blind, placebo-controlled crossover study. J Clin Psychiatry 2007;68:1031–1037.