Tardive Dyskinesia

Centers for Medicare and Medicaid Services (CMS)-Recognized Compendia Data

Neurocrine BIOSCIENCES

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Disclosures

- This information is being provided in response to an unsolicited request for medical information
- This is a summary of treatments used off-label for tardive dyskinesia based on Centers for Medicare and Medicaid Services (CMS) compendia data

Amantadine

Compendia	Information on Treatment of TD[1-4]
AHFS	"There is no evidence that the drug is effective in the treatment of … tardive dyskinesia or other neurological diseases."
Clinical Pharmacology	No data provided
DrugDex	"Although amantadine has been demonstrated in animal studies to prevent dopaminergic neuronal denervation hypersensitivity, human studies have not clearly demonstrated any benefit of amantadine in the treatment or prophylaxis of tardive dyskinesia."
Lexi-Drugs	No data provided

Benztropine

Compendia	Information on Treatment of TD[1-4]
AHFS	"For the symptomatic relief of antipsychotic agent-induced extrapyramidal reactions (except tardive dyskinesia)…" "Benztropine should not be used in patients with tardive dyskinesia, since the drug generally does not relieve signs and symptoms of this condition and may aggravate them."
Clinical Pharmacology	"Benztropine is not recommended for use in patients with tardive dyskinesia" "According to the treatment guidelines of the American Academy of Neurology, there is insufficient evidence to determine the effectiveness of anticholinergic drugs in treating extrapyramidal symptoms such as tardive dyskinesia."
DrugDex	"Benztropine is not indicated in the treatment of tardive dyskinesia Antiparkinsonian agents, such as benztropine, may aggravate symptoms of tardive dyskinesia."
Lexi-Drugs	"Not recommended for use in patients with tardive dyskinesia; benztropine does not relieve symptoms of tardive dyskinesia and may potentially exacerbate symptoms."

Clonazepam

Compendia	Information on Treatment of TD[1-4]
AHFS	No data provided
Clinical Pharmacology	No data provided
DrugDex	No data provided
Lexi-Drugs	“Data from a limited number of patients in a double-blind, randomized, placebo-controlled crossover trial suggests that clonazepam may be beneficial for the treatment of TD. Additional data may be necessary to further define the role of clonazepam in this condition. Based on AAN guideline for the treatment of tardive syndromes, clonazepam given for TD is probably effective in decreasing TD symptoms in the short-term (approximately 3 months) and is suggested for the short-term treatment of TD.”

Tetrabenazine

Compendia	Information on Treatment of TD[1-4]
AHFS	"Although tetrabenazine has only been approved in the US for the symptomatic management of chorea associated with Huntington's disease, the drug has been used with some success for the symptomatic management of other hyperkinetic movement disorders, including …. and tardive dyskinesia." "Clinical experience with tetrabenazine in tardive dyskinesia suggests that the drug is effective in the management of this condition, including in some severe and/or refractory cases."
Clinical Pharmacology	"Tetrabenazine appears to have the best effect in HD but has shown improvement in other hyperkinetic movements disorders, such as tardive dyskinesia (TD), dystonia, Tourette's syndrome, and myoclonus. Tetrabenazine may also have synergistic effects when used in combination with the dopamine antagonist pimozide. One case report describes the successful use of tetrabenazine as part of combination therapy to treat refractory orofacial tardive dyskinesia." "Because tetrabenazine can increase the risk of depression and suicidal thoughts and behavior, the benefit of tetrabenazine should be weighed against the risks of treatment, particularly in those with a history of depression or suicidal attempts or ideation. In addition, HD patients may be predisposed to develop tardive dyskinesia with typical dopamine antagonists; however, tetrabenazine has never been reported to cause TD."
DrugDex	Non-FDA Uses - Tardive Dyskinesia "Effective in 50% or more of patients in several studies Good efficacy in patients unresponsive to prior regimens Adult: a) Oral tetrabenazine in doses up to 200 milligrams (mg) daily has abolished or reduced dyskinetic movements in at least half of patients with tardive dyskinesia, including those unresponsive to prior treatment; many patients continued to receive neuroleptics during tetrabenazine therapy. Efficacy was comparable to that of haloperidol in one small comparison. b) Tetrabenazine 25 mg two to four times daily for one week abolished facial (presumably oral) dyskinesia induced by phenothiazines (chlorpromazine, trifluoperazine) in 3 of 6 elderly patients in a placebocontrolled study. Dyskinesias reappeared within several days of discontinuing therapy. c) In a larger study (n=44), marked reduction in abnormal movements (with excellent functional improvement) was seen in 14% of patients with tardive dyskinesia unresponsive to prior therapy; 57% demonstrated moderate reduction of abnormal movements and good functional improvement. Tetrabenazine was administered for a mean of 21 months. The initial dose was 25 mg daily, with increases by 25 mg daily until 100 mg daily was reached or adverse effects intervened; patients were subsequently titrated based on response (maximum daily dose range, 25 to 200 mg)." Section: Place in Therapy "b) Tetrabenazine has also been studied for the treatment of tardive dyskinesia, either as initial therapy or in patients who have responded poorly to other agents (eg, reserpine, bromocriptine, clozapine). Indirect comparisons suggest tetrabenazine may be the most effective agent available for this disorder, although further studies assessing longterm benefit and the propensity of the drug to aggravate the tardive dyskinesia are needed."
Lexi-Drugs	"Data from a limited number of patients studied suggest that tetrabenazine may decrease the frequency and severity of tardive movements in patients with tardive dyskinesia. Additional data may be necessary to further define the role of tetrabenazine in this condition." "Based on American Academy of Neurology guidelines, tetrabenazine is possibly effective and may be considered in the treatment of patients with tardive dyskinesia"

Gingko Biloba

Compendia	Information on Treatment of TD[1-4]
AHFS	No data provided
Clinical Pharmacology	No data provided
DrugDex	No data provided
Lexi-Drugs	“The American Academy of Neurology guidelines for the treatment of tardive syndromes (2013), including tardive dyskinesia syndrome, concludes that gingko biloba extract is probably useful in tardive dyskinesia syndrome treatment, but data are limited to inpatients with schizophrenia.”

Vitamin E

Compendia	Information on Treatment of TD[1-4]
AHFS	"Has been used to reduce the risk of tardive dyskinesia associated with use of antipsychotic agents"
Clinical Pharmacology	"For the treatment of tardive dyskinesia secondary to antipsychotic treatment (recommendation: equivocal/weak with low detailed level of evidence) high dose vitamin E (e.g., >= 1200 units/day PO, given in divided doses) has been used. Treatment should not replace use of accepted strategies for tardive dyskinesia (TD) such as antipsychotic dose reduction. The American Academy of Neurology (AAN) Practice Guidelines consider the data insufficient to support or refute the use of vitamin E in the treatment of TD; however, some data suggest that vitamin E may be more beneficial in patients with early onset TD (within 5 years). Vitamin E appears to have little prospect for harm in appropriately chosen patients and supplementation as part of a treatment strategy may be considered."
Lexi-Drugs	"A meta-analysis of neuroleptic-induced tardive dyskinesia, including 10 studies from 1966 through 2001, showed that vitamin E protected against deterioration but did not improve the symptoms of tardive dyskinesia. A trial evaluating vitamin E 1,200 units/day versus placebo over 12 weeks reported a mean improvement in Abnormal Involuntary Movements Scale (AIMS) scores. In combination with vitamin C 200 mg/day, vitamin E 1,800 mg/day reduced tardive symptoms in a small trial (N = 8). Theoretically, the combination reduces vitamin E radicals formed when vitamin E scavenges oxygen radicals." "The American Academy of Neurology guidelines for the treatment of tardive syndromes (2013), including tardive dyskinesia, concludes that data are conflicting and insufficient to determine the efficacy of vitamin E in the management of tardive dyskinesia syndrome."

Vitamin E

Compendia	Information on Treatment of TD[1-4]
DrugDex	"Non-FDA Use: Has reduced involuntary movements in patients with tardive dyskinesia in some, but not all, studies: 1) Vitamin E treatment reduced involuntary movements in Chinese patients with tardive dyskinesia (TD). In a randomized, double-blind, placebo controlled trial, 22 patients were given vitamin E, 800 international units/day for the first week and then 1200 international units/day in 3 divided doses for another 11 weeks, and 19 patients were given placebo for 12 weeks. Mean improvement of Abnormal Involuntary Movement Scale (AIMS) scores was significant in the vitamin E group (about 46%, p less than 0.01) and not in the placebo group (4.3%). Scores for the 2 groups were not different at baseline but were significantly better in the vitamin E group than in the placebo group at week 12 (p less than 0.01). No changes in psychopathology (as measured with the Positive and Negative Syndrome Scale) occurred in either group. Mean values of blood superoxide dismutase (SOD) increased significantly in the vitamin E group (p=0.001) and did not change in the placebo group, suggesting that the beneficial effects of vitamin E may be related to a reduction in free radical activity. 2) The combination of vitamin E and vitamin C was effective in reducing symptoms of tardive dyskinesia in 6 patients (aged 40 to 74) with affective disorders and tardive dyskinesia due to previous neuroleptic treatment. In an open study, the patients were given vitamin E 1800 mg/day and vitamin C 200 mg/day. Every patient showed improvement. At the start of treatment, ratings on a dyskinetic movement scale (ESRS) ranged from 20 to 28. After 1 month of treatment, ratings ranged from 7 to 16. The ESRS ratings of the one patient who was followed for 2 years dropped from 24 to 3. The combination of the 2 vitamins is thought to eliminate the possible prooxidative effect on low-density lipoproteins caused by high dose vitamin E monotherapy. 3) In a placebo controlled clinical trial, vitamin E 800 international units twice daily for 2 months produced significant decreases in symptoms of tardive dyskinesia (TD) [129]. Using the modified Abnormal Involuntary Movement Scale (mAIMS), a statistically significant decrease in the total mAIMS (p less than 0.03) and limb truncal mAIMS (p less than 0.006) occurred in vitamin E treated but not placebo treated patients; however, the difference on the orofacial mAIMs was not statistically significant. Patients with TD of less than 5 years duration showed decreases in the mAIMs of 35% vs 11% for patients with TD for more than 5 years. Patients in the vitamin E group received about a 50% lower dose of neuroleptic than patients in the placebo group. Thirty-five patients were enrolled in this study. 4) Vitamin E treatment was associated with improvement in tardive dyskinesia a (TD), with greatest improvements in patients with shorter durations of TD. Fifteen patients (9 with chronic schizophrenia, 6 with schizoaffective disorder) with a history of TD persisting for at least 1 year (average 2.6 years) received placebo or alpha tocopherol 400 international units daily. This regimen was gradually increased over a 2week period to 400 international units 3 times daily for 2 more weeks. Previous regimens of anticholinergic and neuroleptic medications were maintained if possible. A 50% or more reduction in the Abnormal Involuntary Movement Scale (AIMS) score was considered a favorable response. Twelve patients also completed a second trial of placebo and alpha tocopherol. AIMS scores decreased significantly during the alphatocopherol phases of the trials, while no significant decrease was observed with placebo. While only 7 patients experienced a 50% or better reduction in AIMS scores, an overall average decrease in AIMS scores was 43% in patients receiving alpha tocopherol. Patients who displayed a 50% or greater reduction in AIMS score had a shorter history of TD and later onset of psychiatric illnesses than those individuals with a reduction of AIMS score of less than 50% [132]. Similar results were found by others [131]. A significantly lower AIMS score rating (18.5%) was observed in patients with a less than 5year history of TD receiving vitamin E as compared with placebo." Summary: Has reduced involuntary movements in patients with tardive dyskinesia in some, but not all, studies. Patients with tardive dyskinesia of shorter duration more responsive. The combination of vitamin E and vitamin C was effective in reducing symptoms of tardive dyskinesia in patients in a small study.

References

1. *American Hospital Formulary Service Drug Information*. Bethesda: The American Society of Health System Pharmacist, Inc, 2016. Print.
2. Clinical Pharmacology. Retrieved December 2nd, 2016 from www.clinicalpharmacology.com
3. DrugDex. Retrieved November 2nd, 2016 from www.micromedex.com/compendia
4. Lexi-Drugs. Retrieved November 2nd, 2016 from http://www.wolterskluwercdi.com/lexicomp-online/

Back-up

2013 AAN Guideline for Treatment of Tardive Syndrome, including TD

Classification of Recommendation	Definition
Level A	"Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)"
Level B	"Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)"
Level C	"Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)"
Level U	"Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven."

Bhidayasiri R. et al. Evidence-based Guideline: Treatment of Tardive Syndromes. American Academy of Neurology. 2013;82:463-469

Centers for Medicare and Medicaid Services (CMS)-Recognized Compendia

- Definition: "as a comprehensive listing of FDA-approved drugs and biologicals or a comprehensive listing of a specific subset of drugs and biologicals in a specialty compendium, for example, a compendium of anti-cancer treatment."

- A compendium:
  - (1) includes a summary of the pharmacologic characteristics of each drug or biological and may include information on dosage, as well as recommended or endorsed uses in specific diseases;
  - (2) is indexed by drug or biological. See 42 C.F.R. § 414.930(a); 72 Fed. Reg. 66222, 66404.

Desirable Compendium Characteristics

- 1. Extensive breadth of listings.
- 2. Quick processing from application for inclusion to listing.
- 3. Detailed description of the evidence reviewed for every individual listing.
- 4. Use of pre-specified published criteria for weighing evidence.
- 5. Use of prescribed published process for making recommendations.
- 6. Publicly transparent process for evaluating therapies.
- 7. Explicit "Not recommended" listing when validated evidence is appropriate.
- 8. Explicit listing and recommendations regarding therapies, including sequential use or combination in relation to other therapies.
- 9. Explicit "Equivocal" listing when validated evidence is equivocal.
- 10. Process for public identification and notification of potential conflicts of interest of the compendia's parent and sibling organizations, reviewers, and committee members, with an established procedure to manage recognized conflicts.