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Treatment of tardive dyskinesia: A systematic review (1997-2011)

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ABSTRACT – *Background and Objectives:* Tardive dyskinesia (TD) is a frequent and incapacitating side effect of first-generation antipsychotics. Although second-generation antipsychotics (SGAs) seem to be associated with a decreased risk of TD, it remains a severe, unresolved iatrogenic condition. Moreover, there is no commonly accepted effective treatment for TD.

We conducted a systematic review of the literature to assess evidence regarding the effectiveness of different therapeutic interventions for TD.

Methods: We performed a systematic review focussing exclusively on randomised controlled trials (RCTs). We searched the MEDLINE database (1997 to 2011) using the keyword "tardive dyskinesia" within the "title" search field. Twenty-six RCTs were included. Based on the evidence from RCTs, we built a decision tree that healthcare professionals can use to choose an effective therapeutic intervention for TD.

Results: Four therapeutic interventions were found to be effective in TD (vitamin B6, ginkgo biloba, branched-chain amino acids, and piracetam).

Conclusions: Patients with TD could benefit from the therapeutic interventions supported by the data accumulated from RCTs.

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Background

Tardive dyskinesia (TD) causes severe social and physical disability. TD is characterised by abnormal involuntary movements of the tongue, jaw, trunk, or extremities that persist for at least 4 weeks. The symptoms appear during neuroleptic treatment or within 4 weeks after discontinuing neuroleptic treatment that has been administered for at least 3 months. The annual incidence of TD varies between 4 and 5% in patients using first-generation antipsychotics (FGAs)[1]. The use of second-generation antipsychotics (SGAs) is associated with a reduced rate of TD[2], with an estimated incidence ranging from 2.1 to 4.9%[3,4].

Primary prevention that prevents the disease from occurring remains the best strategy. In the case of TD, the lowest effective dose should be used[5,6] for the shortest amount of time possible[7]. There is also a class effect: SGAs cause fewer cases of dyskinesia[4], and clozapine has not shown any correlation to TD[8]. Moreover, prescribing anticholinergic therapy in patients with acute extrapyramidal symptoms is a risk factor for TD[7].

Currently, there is no evidence supporting the effectiveness of any therapeutic intervention for this illness[9]. Nevertheless, several publications have reported an alleviating effect of some treatments for TD symptoms. This review aims to determine the effectiveness and safety of using these proposed therapeutic interventions for TD.

Objectives

This review aims to determine the effects of any intervention for neuroleptic-induced TD in people with schizophrenia or other chronic mental illness.

Methods

Criteria for considering studies for this review

Types of studies. We included only randomised controlled trials (RCTs) described as single- or double-blind.

Types of participants. We included people suffering from schizophrenia or chronic mental illness, irrespective of diagnosis criteria used, who required neuroleptic medications and developed neuroleptic-induced TD.

Types of interventions. We included trials whose aim was to assess any type of intervention in neuroleptic induced TD.

Types of outcome measures. This paper reviewed four health outcome measures that were commonly used in the selected RCTs to assess changes in patients. To determine clinical relevance, we defined significant change using the original cut-off point chosen by the authors.

- Tardive dyskinesia: No significant change in TD score; average endpoint TD score; average change in TD score.
- Mental state: No significant change in mental state; average endpoint mental state score; average change in mental state score.
- Adverse effects: Clinically important adverse effects; any adverse effect.
- Leaving the study early for general reasons.

Search method for identification of studies

A comprehensive systematic literature review was undertaken using electronic database search engines. We searched the MED-

LINE database for articles published between 1997 and 2011 using the keyword "tardive dyskinesia" in the "title" search field. We considered all of the clinical trials returned by this search.

Data collection and analysis

Selection of studies. Two of the authors (MA, WEH) independently and manually inspected the search results to retrieve those studies that were likely relevant. Where disagreement existed, we tried to resolve it by discussion. If a disagreement could not be resolved, we included the trial with a description of the ambiguity in the results section.

Data extraction and management. Two authors (MA, WEH) extracted data independently. In cases of disagreement, we tried to achieve resolution via discussion. If doubt persisted, we did not use the data and mentioned the lack of information. We assessed outcomes using quantitative (i.e., TD score change) or qualitative data (no significant change or significant change in TD score). When it was possible, we used binary data. Participants were divided into "clinically improved" or "not clinically improved" according to the primary cut-off point presented by the authors.

Assessment of risk of bias in included studies

The various risks of bias were evaluated as low, high, or uncertain, using the tool published in the Cochrane Collaboration Handbook[10]. For assessing the risk of bias, this tool recommends that evaluators pay attention to the sequence generation, the allocation concealment, the blinding of participants, the completeness of information, and the risk of selective reporting.

Measures of treatment effect

For continuous data, we calculated the effect size and the 95% confidence interval according to Hedges and Olkin's formula[11]. When binary data were presented, we calculated a relative risk and its 95% confidence interval[12]. When results were significant, we used the tool provided in Grade Profiler 3.6 software (ims.cochrane.org) to determine the absolute risk reduction (ARR) and its 95% confidence interval. The number needed to treat (NNT) and its 95% confidence interval were calculated as the inverse of the ARR.

Unit of analysis issues

Some studies used randomisation by clusters, leading to a significant risk of type I error, reducing the level of evidence provided by the test. In crossover trials, there is a risk of a persistent effect between the two phases despite the wash-out period. This risk is reasonable in the case of chronic patients in stable condition, in an attempt to reduce variance and to increase effective sample size.

Dealing with missing data

The rate of loss affects the credibility of published data. We excluded data from studies where more than 50% of the participants in any group were lost to follow-up.

Results

Selected references

Our search of the MEDLINE database returned 81 references; among these, only 41 articles described therapeutic interventions for symptoms of TD. After controlling for the inclusion criteria, this review included a to-

Table 1
Description of the 26 included and 15 excluded studies

Studies	Year	N	Age (years)	Length	Intervention evaluated
Included studies					
Dorevitch *et al*. (25)	1997	40	64,4	8 weeks	Vitamin E
Sajjad (26)	1998	20	67,8[1]	7 months	Vitamin E
Adler *et al*. (27)	1998	40	61,1[1]	8 weeks	Vitamin E
Adler *et al*. (28)	1999	158	50,7[1]	12 months	Vitamin E
Zhang *et al*. (29)	2004	41	54,5[1]	12 weeks	Vitamin E
Hayashi *et al*. (30)	1997	38	64,6[2]/63,7[2]	5 weeks	Mianserine / trazodone
Angus *et al*. (31)	1997	16	65	3 weeks	Amantadine
Pappa *et al*. (32)	2010	22	52	2 weeks	Amantadine
Cowen *et al*. (33)	1997	33	38[3]/77,3[3]	3 weeks	Acetazolamide + thiamine
Mosnik *et al*. (34)	1997	18	44,1	1 day	Phenylalanine
Shamir *et al*. (35)	2000	19	74	4 weeks	Melatonin
Shamir *et al*. (36)	2001	22	64,2	6 weeks	Melatonin
Lerner *et al*. (37)	2001	15	28-71[4]	4 weeks	Vitamin B6
Lerner *et al*. (38)	2007	50	47	4 weeks	Vitamin B6
Wonodi *et al*. (39)	2004	14	47	4 weeks	Naltrexone
Bai *et al*. (40)	2003	49	50,2	12 weeks	Risperidone
Emsley *et al*. (41)	2004	45	49,7	50 weeks	Quetiapine/Haloperidol
Chan *et al*. (42)	2010	60	42,7[5]/48[5]	24 weeks	Risperidone/Olanzapine
Richardson *et al*. (43)	2003	52	48,0	3 weeks	Branched-chain amino acids
Emsley *et al*. (44)	2006	84	42,9	12 weeks	Eicosapentanoic acid
Caroff *et al*. (45)	2007	35	56,4	12 weeks	Galantamine
Libov *et al*. (46)	2007	40	47	4 weeks	Piracetam
Woods *et al*. (47)	2008	50	45,1[1]	12 weeks	Levetiracetam
Ogunmefun *et al*. (48)	2009	7	62,2	4 weeks	Donepezil
Zhang *et al*. (49)	2011	157	45,3	12 weeks	Ginkgo biloba
Damier *et al*. (50)	2007	10	45,1		Deep brain stimulation
Excluded studies					
Spivak *et al*. (51)	1997	20	43,1	18 weeks	Clozapine
Bassitt&Louza Neto (52)	1998	7	28,5	24 weeks	Clozapine
Kinon *et al*. (53)	2004	95	48,5	8 months	Olanzapine
Bai *et al*. (54)	2005	40	49,6	48 weeks	Risperidone
Lerner *et al*. (55)	1999	5	NS	4 weeks	Vitamin B6
Ondo *et al*. (56)	1999	20	65,2	3 months	Tetrabenazine
Sirota *et al*. (57)	2000	20	69,8	12 weeks	Ondansetron
Michael *et al*. (58)	2002	6	57,8	1 month	Vitamins E & C
Hardoy *et al*. (59)	2003	30	49,7	1 year	Gabapentin
Richardson *et al*. (60)	2004	6	13	2 weeks	Branched-chain amino acids
Bona (61)	2006	17	50	6 months	Levetiracetam
Meco *et al*. (62)	2006	16	69	3 months	Levetiracetam
Konitsiotis *et al*. (63)	2006	8	55,1	1 month	Levetiracetam
Lee *et al*. (64)	2007	69	49	16 weeks	Kamishoyosan
Miyaoka *et al*. (65)	2008	22	57,1	12 weeks	Yi-gan-san

[1] Treatment group; [2] Mianserin vs. trazodone groups; [3] Younger vs. older patient groups; [4] Range;
[5] Risperidone/olanzapine groups.

tal of 26 references. We excluded 15 studies due to a lack of randomisation protocol.

Design. Fourteen trials used a crossover design; 12 were conducted in parallel groups.

Participants. Participants suffered from psychiatric disorders, most often schizophrenia or schizoaffective disorder (18 trials).

Study location. Most of the studies were carried out exclusively among inpatients (17 trials).

Outcomes. The studies often reported outcomes in the form of scale-derived scores. TD was assessed using three different scales: the Abnormal Involuntary Movement Scale (AIMS)[13], the dyskinesia subscale of the Extrapyramidal Symptom Rating Scale (ESRS)[14], and the Maryland Psychiatric Research Center Involuntary Movement Scale (MPRC)[15]. Other extrapyramidal symptoms were assessed using the ESRS, the Simpson-Angus Scale (SAS)[16], and the Barnes Akathisia Rating Scale (BARS)[17]. Mental state was assessed using the Brief Psychiatric Rating Scale (BPRS)[18] and the Positive and Negative Syndrome Scale (PANSS)[19]. Other tests used included the Global Assessment of Functioning scale (GAF)[20], the Mini Mental State Examination (MMSE)[21], the Auditory Verbal Learning Test[22], the Continuous Performance Test[23], and the Stroop test[24].

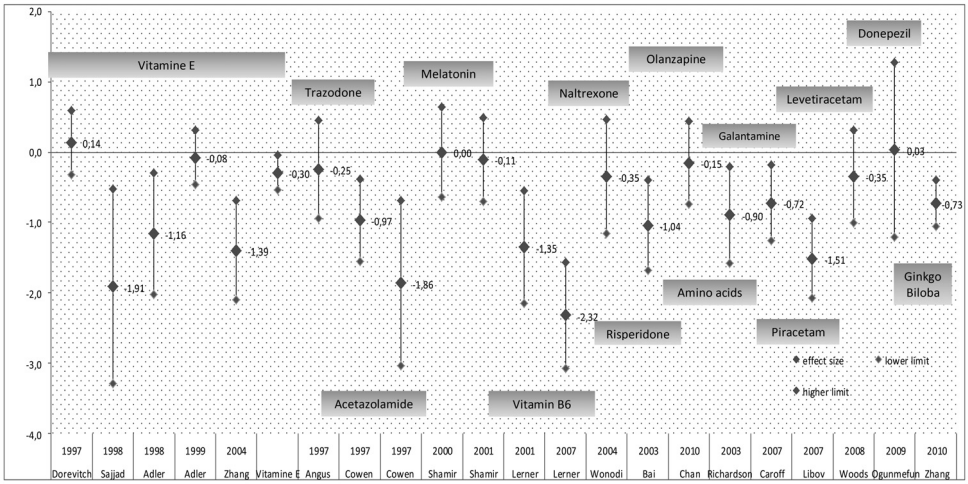

Figure 1. Graphical representation of effect sizes (Hegde's g).

Risk of bias in included studies

Among the selected RCTs, only three studies[29,46,55] concealed the patient allocation. Two active trials had a single-blind design[41,42]; the remaining studies used a double-blind design, although their methods were not always described. The data from the studies often allowed us to calculate the relative risk of leaving the study early. We were not able to use data from two of the studies due to poor presentation[30,32].

Effects of interventions

The efficacy of the different interventions in treating the symptoms of TD is summarised in Tables 2 and 3. Three studies supported the efficacy of vitamin E[26,27,29]. We found evidence for a modest efficacy of vitamin E in the TD scores (five trials, n = 249, Hedge's g effect size (ES) = -0.30, 95% CI = -0.54 to -0.05). We did not find any evidence supporting the efficacy of amantadine, phenylalanine, melatonin, naltrexone, eicosapentanoic acid, donepezil, or levetiracetam in the TD scores. The published data concerning mianserin and trazodone were poorly presented and unusable. We found a significant difference in the average endpoint TD scores for acetazolamide, thiamine, vitamin B6, branched-chain amino acids, galantamine, piracetam, and ginkgo biloba.

Three trials assessed the action of SGAs in TD. Risperidone was compared to a placebo[40] and olanzapine[42], and quetiapine was compared to haloperidol[41]. We found a significant difference between the average endpoint AIMS scores of risperidone and placebo (ES = -1.09, 95% CI = -0.39 to -0.96). Risperidone and olanzapine had significantly different effects (p = 0.55), but they did not produce different clinical improvements in TD (RR = 0.84, 95% CI = 0.55 to 1.30). Quetiapine did not show a clinical improvement compared with haloperidol (RR = 0.64, 95% CI = 0.31 to 1.32).

One study evaluated the efficacy of bilateral pallidal stimulation in resistant TD[50]. The two conditions of stimulation (on-off) were applied to patients over 2 days under double-blind conditions. The authors did not publish the results obtained for blind conditions.

Mental state. Mental state was evaluated by the BPRS in five studies[28,30,40,42,45], the PANSS in three studies[41,44,49], and the MMSE in one study[45]. This review did not find any significant results from additional treatments on psychiatric symptomatology.

Adverse effects. Extrapyramidal symptoms were evaluated by the BARS in two studies[28,45], the SAS in three studies[28,33,45], and the ESRS in four studies[37,38,40,46]. The improvement in parkinsonism was significant for vitamin B6 at doses of 400 mg (ES = -1.58, 95% CI = -2.36 to -0.73)[37] and 1200 mg (ES = -7.61, 95% CI = -9.13 to 5.83)[38]. There was a significant worsening of extrapyramidal symptoms with galantamine (ES = 3.33, 95% CI = 2.50 to 4.08). There was no difference in akathisia scores (ES = 0, 95% CI = -0.52 to 0.52). In all other cases, the extrapyramidal symptomatology remained unchanged. No other severe adverse effects were found in this review.

Leaving the study early. The risk of leaving the study early was noted in most articles included in this review. This risk was not significantly different among the groups included in each trial.

Discussion

Summary of main results

This review suggests that there are scant evidence-based data supporting the efficacy of pharmacological or non-pharmacological interventions for treating TD.

By modifying the balance of dopamine and serotonin in the basal ganglia, 5HT2A antagonism is expected to reduce the symptoms of dyskinesia[66,67]. SGAs showed superior efficacy to placebos[40], but not to FGAs, for this indication[41]. Moreover, an improvement with risperidone was maintained over a period of 48 weeks under open-label conditions[54].

Table 2
Continuous data: mean difference [range] and effect size calculation [range] for TD

Authors, year	Outcome	Intervention	Mean difference	Effect size Hedges's g
Dorevitch *et al*., 1997 (25)	AIMS	Vitamin E	0,50 [-1,17; 2,17]	0,14 [-0,32; 0,59]
Sajjad, 1998 (26)	AIMS	Vitamin E	-6,89 [-11,07; -2,71]	-1,98 [-3,38; -0,59]
Adler *et al*., 1998 (27)	AIMS	Vitamin E	-3,30 [-5,62; -0,98]	-1,16 [-2,02; -0,30]
Adler *et al*., 1999 (28)	AIMS	Vitamin E	-0,30 [-1,83; 1,23]	-0,08 [-0,46; 0,31]
Zhang *et al*., 2004 (29)	AIMS	Vitamin E	-2,31 [-3,38; -1,24]	-1,39 [-2,10; -0,68]
Data analysis	AIMS	Vitamin E	-1,03 [-1,88; -0,17]	-0,30 [-0,54; -0,05]
Angus *et al*., 1997 (31)	AIMS	Amantadine	-0,88 [-3,39; 1,63]	-0,25 [-0,94; 0,45]
Cowen *et al*., 1997 (33)	AIMS	Acetazolamide	-3,85 [-6,08; -1,62]	-0,97 [-1,55; -0,38]
Cowen *et al*., 1997 (33)	AIMS	Acetazolamide	-8,63 [-13,34; -3,92]	-1,86 [-3,03; -0,68]
Shamir *et al*., 2000 (35)	AIMS	Melatonin	0,00 [-3,00; 3,00]	0,00 [-0,64; 0,64]
Shamir *et al*., 2001 (36)	AIMS	Melatonin	-0,50 [-3,25; 2,25]	-0,11 [-0,70; 0,48]
Lerner *et al*., 2001 (37)	ESRS-D	Vitamin B6	-5,07 [-7,80; -2,34]	-1,35 [-2,14; -0,56]
Lerner *et al*., 2007 (38)	ESRS-D	Vitamin B6	-2,70 [-3,37; -2,03]	-2,38 [-3,15; -1,62]
Wonodi *et al*., 2004 (39)	MPRC	Naltrexone	-4,00 [-13,35; 5,35]	-0,35 [-1,16; 0,46]
Bai *et al*., 2003 (40)	AIMS	Risperidone	-5,50 [-8,66; -2,34]	-1,07 [-1,71; -0,42]
Chan *et al*., 2010 (42)	AIMS difference	Risperidone/Olanzapine	-1,20 [-5,77; 3,37]	-0,16 [-0,75; 0,44]
Richardson *et al*., 2003 (43)	Movement count	Amino acids	-107,10 [-86,33; -127,87]	-0,90 [-1,58; -0,21]
Caroff *et al*., 2007 (45)	AIMS	Galantamine	-0,40 [-0,69; -0,11]	-0,72 [-1,26; -0,19]
Libov *et al*., 2007 (46)	ESRS-D	Piracetam	-1,30 [-1,73; -0,87]	-1,51 [-2,07; -0,94]
Woods *et al*., 2008 (47)	AIMS	Levetiracetam	-1,20 [-3,31; 0,91]	-0,38 [-1,04; 0,28]
Ogunmefun, 2009 (48)	AIMS	Donepezil	0,10 [-4,40; 4,60]	0,03 [-1,21; 1,27]
Zhang, 2011 (49)	AIMS	Ginkgo biloba	-2,06 [-2,96; -1,16]	-0,73 [-1,06; -0,40]

Table 3
Binary data: relative risk [range] and number needed to treat (NNT) calculations by intervention.

Study	Intervention	Outcome	Relative risk	NNT
Mosnik *et al.*, 1997 (34)	Phenylalanine	No worsening over 3 points	0,35 [0,18; 0,68]	
Shamir *et al.*, 2001 (36)	Melatonin 10 mg	No clinically significant improvement	0,71 [0,53; 0,96]	3,61 [2,23 ; 26.32]
Lerner *et al.*, 2007 (38)	Vitamin B6 1200 mg	No improvement over 60%	0,66 [0,53; 0,82]	2,94 [2,13 ; 5,56]
Lerner *et al.*, 2007 (38)	Vitamin B6 1200 mg	No improvement over 40%	0,39 [0,27; 0,57]	1,64 [1,37 ; 2,33]
Lerner *et al.*, 2007 (38)	Vitamin B6 1200 mg	No improvement over 20%	0,16 [0,08; 0,34]	1,32 [1,21 ; 1,68]
Bai *et al.*, 2003 (40)	Risperidone	No significant improvement (3 points)	0,32 [0,14; 0,74]	2,10 [1,66 ; 5,49]
Emsley *et al.*, 2004 (41)	Quetiapine/Haloperidol	No improvement over 50% CGI dyskinesia	0,64 [0,31; 1,32]	
Chan *et al.*, 2010 (42)	Risperidone/Olanzapine	No improvement over 50% AIMS	0,84 [0,55; 1,30]	
Emsley *et al.*, 2006 (44)	Eicosapentanoic acid	No improvement in CGI dyskinesia over 30%	0,82 [0,58; 1,17]	
Zhang *et al.*, 2011 (49)	Ginkgo biloba	No significant improvement (30%)	0,51 [0,41; 0,65]	2,15 [1,05 ; 3,01]

We found a positive effect of branched-chain amino acids in one study[43]. This intervention appears safe but is supported by low-quality evidence.

We found evidence for the efficacy of piracetam for TD and parkinsonian symptoms in one study[46]. We assessed the evidence provided by this study as low quality. Thus, piracetam, whose safety is well established, might be a reasonable treatment for TD.

Two trials reported the efficacy of vitamin B6 in reducing the symptoms of TD[37,38]. At a dose of 1200 mg/day, the results were significant, regardless of the threshold used (AIMS score improvement of 60%, 40%, or 20%). The NNT to obtain an improvement of 60% was estimated at 2.88. Therefore, vitamin B6 appears to be a treatment supported by low-quality evidence.

Ginkgo biloba was found to be effective in treating the symptoms of TD in one study[49] with medium-quality evidence. The NNT to obtain greater than 30% symptomatic improvement was calculated at 2.16 subjects. Thus, ginkgo biloba offers a positive benefit-to-risk ratio in TD.

Only a modest benefit of vitamin E in TD has been shown, with contradictory results from different studies. Furthermore, a previous review did not find a clinically significant improvement in patients treated with vitamin E[68]. Thus, we are not able to recommend the use of vitamin E for TD.

One trial determined acetazolamide to be effective in treating TD[33]. The quality of evidence was very low due to the very small sample size. Thus, the efficacy of acetazolamide is not supported by a sufficient amount of reliable data.

Melatonin was not found to be effective at a dose of 2 mg/day and provided ambiguous results at 10 mg/day. In our opinion, the data

provided do not support a positive effect of melatonin on TD.

One study found a modest efficacy of galantamine for TD[45], which was offset by its deleterious effect on extrapyramidal symptoms. Galantamine does not present a positive benefit-to-risk ratio in TD.

Vitamin B6, ginkgo biloba, piracetam, and branched-chain amino acids have shown significantly greater improvement than placebos in RCTs. The use of ginkgo biloba is supported by medium-quality evidence, while the level of evidence supporting branched-chain amino acids, piracetam, and vitamin B6 is low.

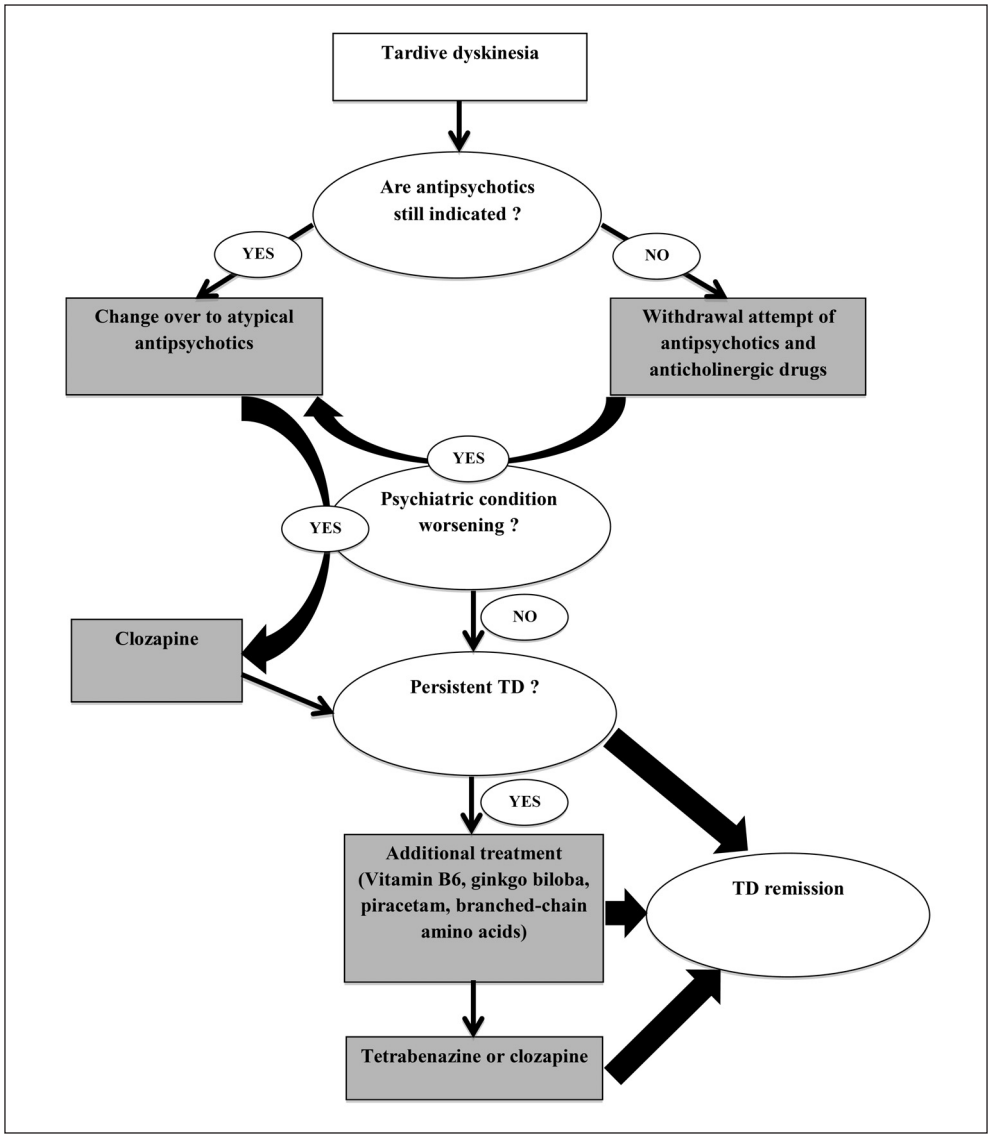

Figure 2. Decision tree for the treatment of tardive dyskinesia.

Treatment strategy for tardive dyskinesia

In light of the data reported above, a medical decision-making pattern can be proposed. It seems necessary to reassess the indications of drug prescriptions and the risk-benefit ratios in the context of iatrogenic disease. Several guidelines recommend the reduction of antipsychotics[1,69,70], though this strategy has not been proven effective in TD[71]. When antipsychotic drugs are definitively indicated, a treatment that is less likely to induce TD should be chosen as the first-line treatment. Risperidone and olanzapine showed comparable efficacy in this indication[40,42,54]. Quetiapine did not demonstrate significantly greater efficacy than haloperidol[41]. Clozapine remains a second-line treatment due to the lack of RCTs.

Four treatments evaluated in this review in addition to antipsychotic medications have shown relative efficacy for the symptoms of TD. Vitamin B6, ginkgo biloba, piracetam, and branched-chain amino acids can all be used in cases of persistent dyskinesia after a disabling relay by SGAs or neuroleptic discontinuation.

The known risk of peripheral neuropathy with high doses of pyridoxine requires long-term monitoring. Nevertheless, the authors did not describe any adverse events for a dose of 1200 mg for 12 weeks[38]. Furthermore, because the safety of the prolonged use of doses below 500 mg has been established, vitamin B6 may be recommended at this dose in cases of persistent symptoms[72]. The use of ginkgo biloba, piracetam, and branched-chain amino acids does not present any particular risk.

In cases of insufficient effects of one or more of these treatments, other therapeutic options that have not been evaluated in RCTs are available. Tetrabenazine, which is already used for several movement disorders, and clozapine are commonly used by physicians in clinical practice. Some uncontrolled studies have reported the efficacy of tetrabenazine in TD[73].

Considering the data presented in this review, we propose a decision tree to help clinicians choose a treatment for patients suffering from TD.

Limitations

Since the description of TD in 1957[74], no effective treatment has been clearly identified. This problem remains important despite the prescription of SGAs at lower doses. The studies included in this review provide a level of evidence that is low to moderate, and they suffer from crucial limitations and imprecision. Each trial included only a small number of participants, and their results have not been reproduced.

Many treatments used experimentally in TD have not been evaluated by RCTs. The use of clozapine and tetrabenazine is based on empirical data and consistent aetiopathogenic hypotheses. These treatments, prescribed by many physicians in cases of TD, have not yet been evaluated by RCTs. Despite the fact that the neuropathology of TD remains complex and has not been fully elucidated, several theories have been proposed[75] that could lead to the development of new compounds useful in the treatment of TD.

Future research on these treatments, including clozapine and tetrabenazine, could bring about significant changes in TD treatment strategies.

Conclusion

This systematic review of the literature has identified several interventions that could

be useful in the treatment of antipsychotic-induced TD. SGAs appear to be a consistent first-line intervention for patients requiring long-term antipsychotic treatment. However, no study has demonstrated their superiority compared to FGAs in TD. Several additional treatments can benefit patients with TD (vitamin B6, piracetam, branched-chain amino acids, ginkgo biloba). In view of these results, it seems reasonable to offer symptomatic treatment to patients suffering from TD. Future research will be necessary to confirm these results and to evaluate other compounds already prescribed by physicians for TD.

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