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Review Article

Updating the recommendations for treatment of tardive syndromes: A systematic review of new evidence and practical treatment algorithm

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ABSTRACT

Background: Management of tardive syndromes (TS) is challenging, with only a few evidence-based therapeutic algorithms reported in the American Academy of Neurology (AAN) guideline in 2013.

Objective: To update the evidence-based recommendations and provide a practical treatment algorithm for management of TS by addressing 5 questions: 1) Is withdrawal of dopamine receptor blocking agents (DRBAs) an effective TS treatment? 2) Does switching from typical to atypical DRBAs reduce TS symptoms? 3) What is the efficacy of pharmacologic agents in treating TS? 4) Do patients with TS benefit from chemodenervation with botulinum toxin? 5) Do patients with TS benefit from surgical therapy?

Methods: Systematic reviews were conducted by searching PsycINFO, Ovid MEDLINE, PubMed, EMBASE, Web of Science and Cochrane for articles published between 2012 and 2017 to identify new evidence published after the 2013 AAN guidelines. Articles were classified according to an AAN 4-tiered evidence-rating scheme. To the extent possible, for each study we attempted to categorize results based on the description of the population enrolled (tardive dyskinesia [TD], tardive dystonia, tardive tremor, etc.). Recommendations were based on the evidence.

Results and recommendations: New evidence was combined with the existing guideline evidence to inform our recommendations. Deutetrabenazine and valbenazine are established as effective treatments of TD (Level A) and must be recommended as treatment. Clonazepam and *Ginkgo biloba* probably improve TD (Level B) and should be considered as treatment. Amantadine and tetrabenazine might be considered as TD treatment (Level C). Pallidal deep brain stimulation possibly improves TD and might be considered as a treatment for intractable TD (Level C). There is insufficient evidence to support or refute TS treatment by withdrawing causative agents or switching from typical to atypical DRBA (Level U).

1. Introduction

Recognized > 50 years ago, tardive syndromes (TS) are common disorders affecting approximately one-third of outpatients with schizophrenia treated with antipsychotics. However, its treatment remains a challenge for physicians mainly due to the small number of evidence-based therapeutic options available and the variable responses of individual patients. The diversity of therapeutic evidence, ranging from case reports, case series, and open-label studies, to randomized controlled trials (RCT), is compounded by the generally small number of patients in most studies and the ability of clinicians to apply the various assessment methods into their clinical practice. In 2010, the American Academy of Neurology (AAN) empaneled an expert group to develop treatment guidelines by reviewing studies that were related to the treatment of TS with the aim of providing evidence-based practical recommendations for clinicians, which were published in Neurology in 2013 [1]. Under the AAN therapeutic classification scheme and a vigorous review process by 2 panelists, the recommendations were in favor of clonazepam and *Ginkgo biloba* as probably effective and should be considered as treatment of TD and TS respectively (Level B), and amantadine and tetrabenazine (TBZ) as possibly effective and might be considered as treatment of TS (Level C) [1,2]. Together with these recommendations, the AAN also released 2 summaries of all recommendations to assist clinicians in making patient care decisions, and to provide patients with TS and their families with a better understanding of what therapies can help treat tardive syndromes [3,4].

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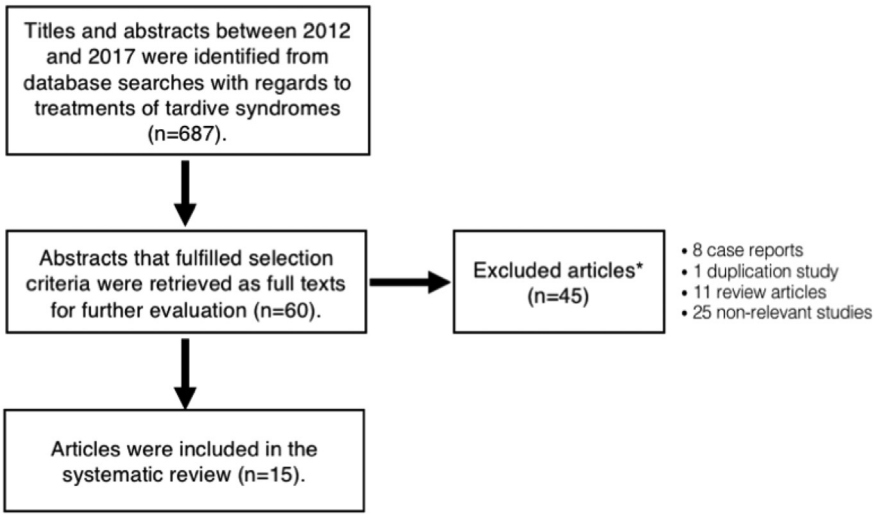

Fig. 1. Summary of the search results.

Following the publication of the AAN evidence-based guideline, it remains clear that treatment of TS is largely unmet. Very few agents have satisfied the AAN's stringent criteria for recommendation as an effective treatment. In fact, none of the available evidence up to 2011 established any treatments of TS as effective (Level A). In addition, since this guideline only provides evidence, it is still challenging for clinicians to understand how to implement these recommendations into daily clinical practice. For example, the current guideline does not provide any information on which agent should be used as first-line or combination treatment. Because further evidence on the treatment of TS has emerged in the 5 years since the guideline's publication, we have undertaken a systematic review of this new evidence with the aim to provide clinicians with updated therapeutic evidence and a practical algorithm on the management of TS.

While TS is an umbrella term for a variety of delayed-onset, persistent motor and nonmotor syndromes associated with dopamine receptor blocking agent (DRBA) exposure, specific syndromes are named based on the predominant manifestation, while recognizing that other phenomenologies may also be present to a lesser extent [5,6]. The “classic” and probably most common form is oral-buccal-lingual (O-B-L) dyskinesia, often used synonymously with the term “tardive dyskinesia” (TD). These are complex repetitive movements that may also affect other body parts, including limbs, trunk, and upper face. Tardive dystonia (TDyst) refers to a dystonic syndrome that may affect any part of the body, and may include some dyskinesia or other phenomenology [7,8]. Tardive akathisia exactly mimics acute akathisia, a syndrome of unpleasant restlessness causing the patient to move constantly [9]. Tardive tics, tardive pain and tardive tremors (TT) also occur. For the purpose of this systematic review, we have evaluated therapeutic evidence for each TS according to what has been described in the literature. For example, if selected studies were described to enroll subjects with TD, the level of evidence and recommendations are limited to TD. However, it is not possible for us to determine in this review if subjects in these selected studies were indeed classical TD populations, or mixed with other TS (e.g. TDyst, TT) unless it was specifically stated in the published report.

2. What is the new evidence on the treatment of tardive syndromes?

2.1. Methods

The systematic review was conducted to address the original 5 questions proposed in the AAN guideline: 1) Is withdrawal of dopamine receptor blocking agents (DRBAs) an effective TS treatment? 2) Does switching from typical to atypical DRBAs reduce TS symptoms? 3) What is the efficacy of pharmacologic agents in treating TS? 4) Do patients with TS benefit from chemodenervation with botulinum toxin (BoNT)? and 5) Do patients with TS benefit from surgical therapy? PsychINFO, Ovid MEDLINE, PubMed, EMBASE, Web of Science and Cochrane were searched to identify evidence published since the search covered by the AAN guideline (1966–2011). Only original, full-text articles published in English between January 2012 and September 2017 that evaluate the treatment of TS were included in this review. Reviews, case reports and editorial articles were excluded. Case series were included if baseline characteristics and period/carry-over effects were clearly presented. The search was supplemented using a bibliography of retrieved articles and the authors' knowledge on this subject. We included studies of the following TS 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 dopamine and noradrenaline systems, vitamin B_6, and vitamin E. Full search terms and methodology are provided as Supplementary data 1. The preferred outcome measures were objective clinical rating scales of TS severity (e.g., Abnormal Involuntary Movement Scale (AIMS)). RB and OJ reviewed abstracts and titles for relevance and rated selected studies using the AAN therapeutic classification scheme (Supplementary data 2) [2,10,11]. Recommendations were linked to the evidence. Level A is the strongest recommendation, established as effective, based on at least 2 consistent class I studies. Level B refers to probably effective treatment, derived from at least one class I study or 2 consistent class II studies. Level C recommendation indicates that the treatment is possibly effective, based on at least one class II study and 2 consistent class III studies. The selected articles were reviewed by the other 2 authors (JF and SF). Disagreements regarding classification were resolved by consensus. A total of 687 titles and abstracts were reviewed, of which 60 full-length articles were selected for further review (Fig. 1). Of those 60 articles, 15 articles fulfilled the selection criteria. To update the existing evidence on the treatment of TS, we also include studies that were listed in the original AAN recommendations, including clonazepam, *Ginkgo biloba*, amantadine, and tetrabenazine (TBZ). A summary of studies with recommendations as effective (Level A, B, and C) is shown in Table 1, categorized by the 5 proposed questions in the management of TS. Supplementary data 3 provides a complete list of studies that were included in the review process.