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Review Article

Future directions in tardive dyskinesia research

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ABSTRACT

Tardive dyskinesia (TD) research is at a crossroads because of renewed interest in this syndrome following the successful development and regulatory approval of two novel vesicular monoamine transport 2 (VMAT2) inhibitors. Despite these clinical advances, significant lacunae exist in the knowledge base of TD pathophysiology, prognosis, and epidemiology. Moreover, conflicting definitions of TD as either a syndrome that encompasses a broad array of related phenomena or as a specific subset of tardive syndromes are an impediment to both clinical and basic science research, and to educational efforts targeting nonspecialist clinicians. A unique opportunity is thus presented by the enhanced focus on TD to resolve fundamental issues with regards to nomenclature and clinical criteria, thereby facilitating more sophisticated surveillance and genetic and epidemiological research into tardive movement disorders related to dopamine receptor blocking agents. The widespread use of newer antipsychotics portends that TD will remain a persistent public health issue. This article will present one view of research avenues to be explored for this neuropsychiatric condition, including those that may yield immediate therapeutic benefits by extending expert knowledge into routine clinical care situations.

1. Introduction

The regulatory approval of two novel vesicular monoamine transporter type 2 (VMAT2) inhibitors for the treatment of tardive dyskinesia (TD), valbenazine (VBZ) and deutetrabenazine (DTBZ), has rekindled interest in all aspects of this disorder. Despite lower rates of neurological adverse events with antipsychotics developed in the past 30 years [1], TD is anticipated to remain a persistent issue based on the increasing use of newer dopamine D_2 antagonist and partial agonist medications (henceforth referred to as dopamine receptor blocking agents or DRBAs) for numerous indications beyond schizophrenia and acute mania. The greater availability of effective TD treatment options is a boon to patients and clinicians, and these developments are reflected in a significant uptick in TD-related publications since the nadir earlier this decade (Fig. 1). Yet the increasing focus on this disorder has exposed a number of unresolved issues that demand attention. The current knowledge base surrounding TD is exhaustively reviewed by companion papers in this issue. The purpose of this paper is to outline proposed research opportunities devoted to understanding TD pathophysiology and clinical course, elucidating optimal approaches to educating and assisting clinicians of various backgrounds and specialties in systematically assessing abnormal movements during DRBA exposure, and clarifying the terminology of tardive syndromes to facilitate clinical and biological research. An attempt is made to prioritize these initiatives to the extent that pursuit of certain research areas will be dependent on resolution of other issues.

2. Terminology

Descriptive neurology has a rich tradition [2,3], and it was through detailed observations that distinct syndromes were elucidated [4], and a nosological framework erected based on underlying pathophysiology [5,6]. Importantly, this descriptive vocabulary was critical to defining disorders based not only on pathophysiology (when understood), but on the expected clinical course and response to treatment. Although TD had been recognized since the late 1950s, it was not until the early 1980s that a research-oriented definition was created by Schooler and Kane to examine antipsychotic-associated TD [7]. While prior DRBA exposure and symptom persistence were common to subsequent definitions, the handling of specific manifestations was variably addressed. Pleas for clarity consistently emerged in the literature [8,9], but competing criteria persisted, including the competing views that resulted in the term TD to variably describe either a specific subset of abnormal movements related to DRBA exposure [10], or to a syndrome that encompassed an array of movements including stereotypy, dystonia, akathisia, tics, chorea, myoclonus, and orobuccolingual movements [11].

Consistent and clear terminology is of critical importance at this

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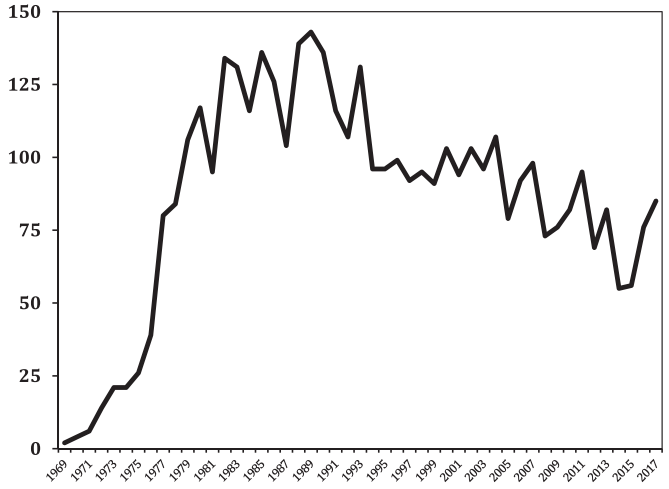

Fig. 1. Tardive dyskinesia references by year January 1, 1968-October 1, 2017. (PubMed data obtained October 1, 2017).

juncture, as a consensus definition is necessary for epidemiologic studies, as well as clinical and educational research. Importantly, in the absence of defining pathophysiology that distinguishes specific manifestations, this definition will drive future algorithmic approaches to DRBA-related movement disorders based on response to the common interventions: minimization of DRBA use (and discontinuation when possible), minimization of anticholinergic antiparkinsonian exposure (and discontinuation when possible), and use of VMAT2 inhibitors.

The Delphi model has emerged as a preferred method for structured decision-making, particularly where the goal is consensus building among a group of experts. The Delphi model was developed by the Rand Corporation in the early 1950s and first utilized to provide expert guidance about the nature and priority of important US industrial sites that could be potential targets for Soviet atomic weapons [12]. The iterative nature of the questioning process and participant anonymity are key features of Delphi that avoid pitfalls of face-to-face discussions wherein group dynamics often interfere with the rational process of consensus discovery. Moreover, it has been used successfully for a variety of medical applications, especially where unclear or competing diagnostic criteria demand resolution.

Recently, the Delphi method was used to establish consensus criteria for neuroleptic malignant syndrome (NMS), a diagnosis whose multiple working definitions had impeded the ability to interpret the clinical literature [13]. The NMS panel included 17 clinicians from psychiatry, neurology, anesthesiology, and emergency medicine, and each was presented with comprehensive reviews of NMS criteria culled from literature published within the prior decade. Based on the panel's preliminary review, 64 distinct NMS clinical criteria were proposed for the initial round of voting. An a priori definition for the consensus endpoint was: a) a $\leq$ 10% change from one voting round to the next in the mean priority score for an individual item; and b) a mean change of $\leq$5% in the absolute-value percentage changes in mean individual item priority scores across all items [13]. Despite the large number of proposed criteria, only 5 rounds of voting were needed to achieve consensus. Importantly, the development of consensus NMS criteria facilitated a subsequent validation study [14].

Table 1 presents a set of key issues in the TD definition that could be resolved using the Delphi method, with other items added based on preliminary input from the panel of experts. The voting group would ideally be composed of equal numbers of psychiatrists and neurologists with sufficient expertise, all of whom would be chosen by an independent entity that maintains anonymity of the chosen experts during the rounds of voting, establishes a priori criteria, oversees the voting process and reports the outcomes. This effort could be framed as a research question in the following manner: Can a consensus definition of tardive dyskinesia be achieved using the Delphi approach? The outcome of this question would inform all clinically related efforts in the field and bring a consistent approach to discussions about prevalence and treatment.

Table 1
Key issues in the definition of tardive dyskinesia to resolve using a Delphi approach.

Issue 1. Global definition

Tardive dyskinesia is one of a number of distinct tardive syndromes (e.g., tardive dystonia, tardive akathisia, etc.) each of which has a characteristic presentation and diagnostic criteria.
OR
Tardive dyskinesia is a diagnosis with marked individual variability in its presentation and may include classical orobuccolingual movements, other stereotypies, dystonia, tics, akathisia, chorea, athetosis, and rarely sensory phenomena.

Issue 2. Minimum extent of clinical symptoms

A diagnosis of tardive dyskinesia is met only when a minimum threshold score is consistently met on a standardized rating instrument (e.g., AIMS) after other confounding movement disorders have been ruled out. (e.g., Schooler-Kane AIMS score criterion: at least moderate in $\geq$1 area, or at least mild in $\geq$2 areas.
OR
A diagnosis of tardive dyskinesia is met with a consistent nonzero score on a standardized rating instrument (e.g., AIMS) after other confounding movement disorders have been ruled out.

Issue 3. Duration of DRBA exposure

A diagnosis of tardive dyskinesia is met only in those with a minimum duration of DRBA exposure (e.g., 1 month or 3 months, or possible variations based on the DRBA nature [first vs. second generation antipsychotics] and patient age [< 65 years old, $\geq$65 years old])
OR
A diagnosis of tardive dyskinesia can be met without a minimum duration of DRBA exposure

Other issues:

a. Duration of symptom persistence required
b. Subjective awareness or distress

3. Clinical phenomenology

The elaboration of a consensus TD definition will subsequently facilitate the collection of epidemiologic data across various sites and countries in a manner previously not possible. While recent studies indicate that TD prevalence using modified Schooler-Kane criteria has remained remarkably stable over the past two decades [15], in some publications tardive dystonia is considered a separate diagnosis [16] based on the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) classification [10]. Moreover, most US-based publications have been generated by academic medical centers [17], leaving enormous gaps in our knowledge of TD incidence and prevalence in nonacademic community mental health and state psychiatric hospital settings [18].

Table 2 presents a starting point for discussions on clinical research opportunities divided into broad categories of prevalence/incidence, screening/education and treatment. Many of these initiatives are mutually interdependent: for accurate prevalence data to be amassed nonspecialist clinicians must either be successfully trained or supported with remote consultation efforts. As of this writing there are no studies available in Medline that report on telemedicine interventions or on the use of new technologies for the diagnosis and management of TD. The success of any educational or consultative approach will also relate to efforts to refine or improve upon the Abnormal Involuntary Movement Scale as the most commonly employed tool for screening and monitoring [9]. A wealth of clinical data is available from videos obtained during trials of the new VMAT2 inhibitors [19–23] that can be used to derive a brief simplified TD screening procedure, and this video repository can also be used to examine whether the AIMS or another instrument is most suitable to track therapeutic response. Moreover, the AIMS lacks standardized definitions for severity ratings. Any refinement to the AIMS or the development of a novel instrument must be wedded