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Integration of technology-based outcome measures in clinical trials of Parkinson and other neurodegenerative diseases

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ABSTRACT

Introduction: We sought to review the landscape of past, present, and future use of technology-based outcome measures (TOMs) in clinical trials of neurodegenerative disorders.
Methods: We systematically reviewed PubMed and ClinicalTrials.gov for published and ongoing clinical trials in neurodegenerative disorders employing TOMs. In addition, medical directors of selected pharmaceutical companies were surveyed on their companies' ongoing efforts and future plans to integrate TOMs in clinical trials as primary, secondary, or exploratory endpoints.
Results: We identified 164 published clinical trials indexed in PubMed that used TOMs as outcome measures in Parkinson disease (n = 132) or other neurodegenerative disorders (n = 32). The ClinicalTrials.gov search yielded 42 clinical trials using TOMs, representing 2.7% of ongoing trials. Sensor-based technology accounted for over 75% of TOMs applied. Gait and physical activity were the most common targeted domains. Within the next 5 years, 83% of surveyed pharmaceutical companies engaged in neurodegenerative disorders plan to deploy TOMs in clinical trials.
Conclusion: Although promising, TOMs are underutilized in clinical trials of neurodegenerative disorders. Validating relevant endpoints, standardizing measures and procedures, establishing a single platform for integration of data and algorithms from different devices, and facilitating regulatory approvals should advance TOMs integration into clinical trials.

1. Introduction

Validated, standardized, and widely used device-based medical measurements, such as heart rhythm recording, blood pressure measurements, and respiratory volumes are widely accepted outcome measures in clinical practice and interventional trials [1]. A new generation of technology-based objective measures (TOMs), including wearable sensors, telemedicine, and computer interface, has emerged for application in the field of neurodegenerative disorders, but validation across proprietary platforms and integration into clinical trials has lagged behind [2].

TOMs, which are defined as the outcomes of device-based instrumented clinical tests conducted by clinicians in standardized environments, or self-administered by patients to detect and monitor impairments in specific functions in everyday life [2], might prove relevant in assessing functional state, disease progression, and response to therapy in patients with neurodegenerative disorders. TOMs can increase the accuracy of endpoints and minimize intra- and inter-rater variability in clinical assessments. Moreover, by reducing the standard deviation of clinical endpoints and simplifying performance of repetitive assessments, TOMs can decrease the sample size of clinical trials, shorten their duration and lower their cost [3–7]. Still, several challenges, such as relevance of measured targets, standardization of extracted parameters, costs, and compliance of patients wearing TOMs, must be addressed.

We sought to review data on the use of TOMs in neurodegenerative disorders from the existing literature, from ongoing clinical trials, and from a survey of medical directors of pharmaceutical companies involved in trials of neurodegenerative diseases. Our

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objective was to provide an updated landscape of the past, present, and future use of TOMs as diagnostic and monitoring tools in neurodegenerative clinical research.

2. Methods

2.1. Literature review

We systematically reviewed the literature for clinical trials using TOMs in neurodegenerative diseases, including but not limited to PD, Alzheimer disease (AD), Huntington disease (HD), and Amyotrophic lateral sclerosis (ALS). PubMed and ClinicalTrials.gov were searched for interventional trials conducted from January 1980 to June 2017, in which technology was used to measure the primary, secondary, or exploratory outcomes.

2.1.1. Participants and interventions

We selected studies involving patients with neurodegenerative diseases. There were no restrictions applied to gender, age, disease duration, type of neurodegenerative disease, or disease severity, nor were limits on the type of intervention, or whether controls were used.

2.1.2. TOMs and domains (endpoints)

TOMs including, but not limited to, accelerometers, actigraphy, gait analysis, brain computer interface, telemedicine, sensors, or remote sensing technology, were considered. Imaging and laboratory instruments for testing human samples and genetics were excluded. The domains assessed by TOMs, such as motor and non-motor endpoints, were also captured.

2.1.3. Data collection and analysis

2.1.3.1. Search methods. We used the search strategy recommended by Cochrane [8]. Relevant articles were identified through electronic search of PubMed and ClinicalTrials.gov using the following keywords: Alzheimer's disease [Mesh], Alzheimer, Parkinson's disease [Mesh], Parkinson, Amyotrophic lateral sclerosis [Mesh], ALS, Huntington disease [Mesh], Huntington, Neurodegenerative disease [Mesh], Diagnosis, Computer-Assisted [Mesh], Decision Making, Computer-Assisted [Mesh], User-Computer Interface [Mesh], Therapy, Computer-Assisted [Mesh], Actigraphy [Mesh], Gait [Mesh], Brain-Computer Interfaces/therapeutic use [Mesh], Brain-Computer Interfaces/utilization [Mesh], Telemedicine/utilization [Mesh], Wireless Technology/utilization [Mesh] (Appendix 1). Duplicated studies were identified by DOI (for PubMed) or specific identification codes (for trials reported in ClinicalTrials.gov) and were removed from the database.

2.1.3.2. Selection of studies. Four authors (C.A.A., M.M., P.L., J.A.V.) screened the abstracts of all search results to identify studies meeting the inclusion criteria. Full-text articles of selected publications were reviewed.

2.1.3.3. Data extraction. The data extracted included: primary, secondary, and exploratory outcomes; TOM(s) used; status of the study (completed or ongoing); type of neurodegenerative disease(s); and study identifier.

2.1.3.4. Data analysis. Interventional trials identified in ClinicalTrials.gov were analysed for the type of TOM(s) used, the type of endpoint assessed by TOMs, categorized as primary, secondary, or exploratory outcome, and the functional domain evaluated by TOMs. In addition, clinical trials indexed in PubMed and meeting the inclusion criteria were divided per year and per disease and reported using descriptive statistics.

2.2. Survey

A survey with 14 questions related to the present and future use of TOMs in clinical trials (Appendix 2) was prepared using a free online survey application (allcounted.com; Rockville, MD, USA). A link with the survey was sent via email to medical directors of 12 different pharmaceutical companies engaged in clinical trials of neurodegenerative diseases.

3. Results

3.1. TOMs utilization in published clinical trials

The search strategy resulted in 947 studies from PubMed from 1980 to 2017. A total of 772 studies did not meet the inclusion criteria and 11 were considered duplicates. Thus, 164 clinical trials were included in this analysis. The target population was PD in 80.5% (n = 132/164), AD in 11.6% (19/164), HD in 1.8% (3/164), ALS in 1.2% (2/164), and other neurodegenerative diseases in 4.9% (8/164). The number of published clinical trials integrating TOMs showed a trend of increase over the years (Fig. 1).

3.2. TOMs and domains measured in ongoing clinical trials

The ClinicalTrials.gov search strategy yielded 42 ongoing clinical trials using TOMs as primary, secondary, or exploratory outcome measure, corresponding to 2.7% of ongoing clinical trials in neurodegenerative diseases (1529). The target population was PD in 54.8% (23/42), AD in 35.7% (15/42), ALS in 7.1% (3/42), and spinocerebellar ataxia (SCA) in 2.4% (1/42) (Fig. 2).

Sensor-based technology (accelerometers and actigraphy) was used in 76.2% (32/42) of trials, assistive technology/telemedicine in 7.1% (3/42), brain computer interface in 7.1% (3/42), GPS-tracking technologies in 4.8% (2/42), and electrophysiological measures in 4.8% (2/42). Endpoints assessed by TOMs were categorized into 13 domains: gait, physical activity, sleep, balance, protocol adherence, tremor, activities of daily living, cognition, electrophysiological measures, bradykinesia, information transfer, movement speed, and speech (Fig. 3).

3.3. TOMs integration into future clinical trials

The survey sent to 12 medical directors from pharmaceutical companies (Appendix 2, 100% response rate) indicated that 83% of them (n = 10) are considering using TOMs in future clinical trials in neurodegenerative diseases within the next 5 years. Half (n = 6) have already used TOMs. One third (n = 4) would apply several sensors into a single integrated platform, regardless of source manufacturer and proprietary platforms; 58% (n = 7) would apply one or two sensors from a single manufacturer, and only 8% (n = 1) would apply two or more sensors from two manufacturers using their separate (non-compatible) proprietary platforms.

4. Discussion

We found that less than 3% of ongoing clinical trials in neurodegenerative disorders (42/1529) are using TOMs as primary, secondary, or exploratory outcome measures, with gait, motor activities, sleep, balance, and tremor accounting for the most assessed domains. Nevertheless, the survey of medical directors from pharmaceutical companies suggested that TOM integration in clinical trials for neurodegenerative diseases will markedly increase within the next 5 years.

These data indicate that TOMs are a promising yet underutilized outcome measures in neurodegenerative disorders, still relegated

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