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Limited responsiveness related to the minimal important difference of patient-reported outcomes in rare diseases

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Abstract

Objectives: To explore the responsiveness of patient-reported outcomes (PROs) in interventional studies involving patients with rare lysosomal storage diseases (LSDs).

Study Design and Setting: We searched eight databases for experimental and nonexperimental studies. Pairs of trained reviewers independently screened articles and subsequently extracted data from the eligible studies. Among studies with 10 or more patients using a valid PRO, we assessed the responsiveness of PROs based on a reanalysis of the data using minimal important difference estimates. Our analyses focused on statistically significant within-group differences in PROs for observational studies or the statistically significant between-group differences in PRO scores for controlled studies.

Results: Of 2,679 unique records, 62 interventional studies addressing patients with Fabry (55%), Gaucher (19%), Pompe (16%), and mucopolysaccharidoses (11%) proved eligible. The most frequently used PROs were the Short-Form-36 (25 studies), Brief Pain Inventory (20 studies), EuroQoL-5D (9 studies), and the Fatigue Severity Scale (6 studies). Observational studies suggest that PROs sometimes detect significant within-group changes when present. Randomized trials raise questions regarding the responsiveness of PROs to small differences between groups.

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Conclusions: Most studies have relied on generic PROs to evaluate quality of life and symptoms in patients with rare LSDs. PROs appear more responsive in observational studies than randomized trials.

Keywords: Responsiveness; Patient-reported outcomes; Minimal important difference; Rare disease; Lysosomal storage disease

1. Background

Lysosomal storage diseases (LSDs) represent a group of genetic diseases affecting adults and children arising from a deficiency of a specific lysosomal protein, or in a few cases, from nonlysosomal proteins that are involved in lysosomal biogenesis [1]. Clinical features of the diseases result from the accumulation of metabolic substrates, and most patients experience substantial neurological involvement with considerable morbidity and a reduced life expectancy [2]. Currently, there are a number of interventions that have demonstrated improved survival and that offer symptomatic management including enzyme replacement therapy, substrate reduction therapy, and bone marrow transplantation [2,3].

Clinical research evaluating medical interventions traditionally addressed survival, cure, major morbid events, and physiological, biological, or laboratory-based measures typically measured by clinicians. Physiological, biological, or laboratory-based outcomes (i.e., surrogates) provide only indirect evidence regarding outcomes of importance to patients [4,5]. To capture patients' perspectives, investigators increasingly rely on subjective or self-reported outcomes that can directly measure symptoms, quality of life, as well as side effects of treatment [6,7]. Patient-reported outcomes (PROs) report the status of the patient's health condition directly from the patient without any interpretation by clinicians or anyone else [8]. PROs enable patients to provide information regarding the consequences of their disease and are often the outcomes of most significance for patients.

Rare diseases pose a unique challenge to clinicians and researchers. Because of their low prevalence, establishing the impact of potential treatments is difficult. When sample sizes are necessarily limited, high instrument responsiveness (i.e., the ability to detect all important effects, even if small) is particularly important. Although researchers have investigated the use of PROs in clinical trials in a variety of areas such as cardiovascular disease [9], rheumatoid arthritis [10], and respiratory disease [11], their use in studies of rare diseases including LSDs is not well established and their potential is unknown. Thus, we undertook a systematic review of the literature to identify studies involving patients with five LSDs to document the nature and responsiveness of PROs compared to surrogates (e.g., creatinine, glomerular filtration rate, left ventricular mass, forced vital capacity) in interventional studies.

2. Methods

2.1. Literature search

In collaboration with an experienced medical librarian, we identified relevant studies published in English with systematic searches of CENTRAL, CINAHL, EMBASE, MEDLINE, PsycINFO, Web of Science, PapersFirst, and ProQuest Dissertations from the inception of each database up to July 2013 [12]. Eligible studies: [1] enrolled patients with at least one of the following five LSDs or LSD subtypes (Gaucher type I nonneuropathic; Anderson-Fabry disease; Pompe disease type II, Niemann-Pick type B or nonneuronopathic, or mucopolysaccharidoses type I and type II); [2] used an intervention in an experimental (randomized or nonrandomized controlled trials) or observational study design (prospective or retrospective cohort, case-control, case reports); [3] used a PRO to quantify patients' symptoms or quality of life.

2.2. Study selection and data extraction

Reviewers worked in pairs to independently screen titles and abstracts and full-text articles to identify eligible articles. Before beginning data extraction, to calibrate reviewers, we paired less with more experienced team members and provided them with four practice articles for abstraction. Subsequently, the reviewers independently extracted data from the eligible studies using a standardized Excel form before meeting to come to consensus on the abstracted items. Data collection included information regarding the study methodology, population, intervention, and outcomes. We did not collect information regarding adverse events or disease-specific severity score indices. We resolved any disagreements via discussion or with the help of a third reviewer.

2.3. Analytical approach

We summarized the nature of identified PROs, including validated generic and disease-specific instruments as well as ad hoc measures used in patients with LSDs. We defined ad hoc PROs as those for which there was no published evidence of psychometric properties. We used anchor or distribution-based minimally important difference (MID) to quantify the responsiveness of PROs in studies with 10 or more patients [12].