

Measuring and interpreting patient-reported outcome data from clinical trials of diabetes medication

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Abstract

Some treatment strategies may negatively impact psychosocial functioning while striving for good clinical and physical outcomes. Patient-reported outcome measures (PROMs) are increasingly incorporated into the clinical development of new treatment to understand the patients' perspective of treatment effects in clinical trials. However, it is sometimes difficult for researchers and healthcare professionals to review PROM data, as meaningful interpretation requires a different mindset from looking at traditional clinical endpoint data. This article provides assistance for reading and interpreting PROM endpoints. It proposes that the reader firstly looks for evidence of no detriment with the experimental therapy, then for improvement, and where study design and prior analyses support it, a comparison of change in PROM scores between the experimental and control therapies. The article provides explanation and rationale for this hierarchy of PROM interpretation.

Keyword: Patient reported outcome measures, clinical trials, diabetes, treatment

Introduction

Diabetes is one of the Western world's most common chronic conditions, with global prevalence increasing rapidly. Type 2 diabetes (T2DM) constitutes 85-95% of diabetes and is accompanied by significant clinical and economic burden [1]. As of the start of 2014 there were 13 classes of therapy licensed and available to treat hyperglycemia in T2DM, with many classes containing multiple medications. Although one may perceive the availability of a wide array of medication as providing flexibility in designing personalized T2DM regimens, for many the choice is overwhelming [2]. In acknowledgement of this, in 2012 the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) convened a joint task force to develop recommendations for therapy highlighting potential sequences of T2DM therapy. As well as providing a loose algorithm for treatment intensification, the ADA/EASD consensus statement clearly highlights that "providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions" is the cornerstone of successful management of T2DM [3]. This requires full understanding, engagement, and commitment of the patient to the prescribed treatment strategy.

Recent meta-analyses have shown that there is little clinically-relevant difference among available therapies in terms of glycemic control [4,5]. However, a comprehensive definition of health is not defined purely by clinical outcomes, but rather by the presence of physical, mental and social well-being [6]

and available therapies do differ in side-effect, safety concerns, mode, method and frequency of administration. Some treatment strategies may therefore negatively impact psychosocial functioning while striving for good clinical outcomes.

How patients perceive their condition and associated treatment as well as the impact it has on their lives is likely to impact on clinical outcomes [7]. This process may be mediated by medication-taking behavior, which in turn may be associated with variables such as regimen burden, complexity, interference of daily activities, pain and embarrassment [8,9]. Asking patients about their perceptions of and experiences with antihyperglycaemic medication can therefore offer potential insights into the subjective experience of therapy [3,10-12] and help clinicians work with patients to define an optimal treatment regimen. The patient perspective can be expressed in a quantifiable and standardized manner by utilizing patient-reported outcome measures (PROMs).

Measuring patient-reported outcomes

PROMs are increasingly incorporated into the clinical development of new T2DM treatment to complement physician evaluations and biological markers of efficacy and tolerability. The PROM directly describes the patient's perception of a disease and its treatment(s) without the interpretation of responses by a physician or anyone else. The term 'PROM' is used as an umbrella term to cover both single dimension and multi-dimension outcome measures evaluating symptoms, quality of life (QoL)/health-related quality of life (HRQL), health status,

impact of treatment on daily life, adherence to treatment and satisfaction with treatment, among others. Each type of PROM represents a different aspect of an individual's experiences, thoughts, and feelings about a condition and/or its treatment. The US and European regulators have released guidance on the use of PROMs in medical product development [13,14], clarifying expectations of PROMs used to describe treatment effects in clinical trials and highlighting the scientific rigour that should be incorporated into the development and selection of PROM endpoints, and a recent PROM extension to the CONSORT statement details how the data should be reported [15-17].

PROMs can be either generic or T2DM-specific. Generic instruments assess concepts that are not disease- or treatment-specific, enabling comparison across various conditions. They are commonly used for health policy and reimbursement decisions. T2DM-specific instruments do not allow comparison with other conditions, but they are likely to be more sensitive to T2DM and are therefore preferable in most circumstances for comparative efficacy/effectiveness research [18,19]. In the UK Department of Health (DoH) PROM Pilot Study, both generic and disease-specific instruments are administered to inform decisions about whether PROMs are an effective way of involving the public and measuring outcomes of the NHS on a large, national scale in individuals with diabetes. To ensure that PROM data are meaningful, it is important that the PROM has evidence of being a reliable and valid measure of the specific concepts targeted in a T2DM population, as well as being sensitive to change, otherwise conclusions will be confounded by measurement error. The selection of PROMs should therefore be systematically undertaken, with consideration to their qualitative and quantitative development. The DHP-18 is the disease-specific instrument selected for the DoH PROM Pilot Study to measure the psychological and behavioural impact of living with diabetes. The DHP-18 was developed with patient samples, has demonstrated reliability and validity, and has well defined scoring guidelines, including the calculation of a clinically relevant minimally important change from baseline [20,21].

Interpreting patient-reported outcomes

When PROMs have been used in comparative clinical research, it is sometimes difficult for researchers and HCPs to understand the meaningfulness of the output, as interpretation requires a different mindset from looking at traditional clinical endpoint data where between-group changes are of primary interest. Rather, the primary consideration when looking at PROM data is ensuring that the selected/experimental treatment strategy does not negatively impact PROMs while striving for good glycaemic control [22]; for example increases in anxiety associated with insulin initiation [23]. Within-group improvements and between group differences are explored thereafter, as explained in the following paragraphs.

PROM data from the experimental treatment cohort should

first be evaluated for no detriment over the course of the clinical study (no worsening of scores within group) using appropriate probabilistic statistical testing and controlling for covariates. Categorical data on the proportion of patients demonstrating no worsening of score in the PROM can be a useful addition to presenting continuous average score change. In a multi-dimension instrument, each dimension should be evaluated individually. For example, the widely-used Diabetes Symptoms Checklist (DSC-r) [24] has 34 items comprising 8 symptom clusters, each measuring a different aspect of diabetes symptomatology; hyperglycaemic, hypoglycaemic, pathophysiological-cognitive, pathophysiological-fatigue, cardiovascular, neurological-pain, neurological-sensory, and ophthalmologic. All items can also be summed together to form a total score, and it is this total score which is most frequently reported in the literature. However, concluding "no detriment in symptoms as demonstrated by no change in mean total DSC-r score" may mask important improvements in some domains and significant worsening in other domains.

With some PROM endpoints, a lack of detriment is a sufficient finding and improvement may not be expected. An example is in the European observational study CHOICE where anxiety and depression were evaluated using a PROM to ensure that the initiation of injectable treatment for T2DM did not increase either measure of psychological outcomes [10]. However, where within-group improvements are hypothesized in the selected/experimental treatment strategy and where "no detriment on average" in relevant PROMs or PROM domains is demonstrated, the data should be presented to understand whether PROM improvements are observed. An example is the study of educational interventions in Germany and Spain [25], where diabetes-related emotional distress improved following conversation maps sessions, despite a reasonably low baseline score. In addition to looking at the significance of the observed within-group change using traditional statistical testing, it is advisable to explore effect sizes (ES) of this change, particularly where the study was not statistically powered for the PROM. Further, a meaningful change in individual patient scores can be identified through calculation of a "minimally important change" (MIC), using clinical anchors to define a responder. The proportion of patients with an improvement of this magnitude can then be reported [26,27]. For completeness, change data can be presented on a cumulative distribution to allow a variety of MICs to be examined simultaneously and collectively [13,28].

Finally, if within group improvement is observed in the selected/experimental treatment cohort, differences between changes in the experimental treatment cohort and the control treatment cohort should be examined. Sometimes, between-group differences would not be hypothesised. For example, a recent study of dulaglutide, an experimental GLP-1 receptor analog, measured treatment satisfaction using a PROM in a double-blind double-dummy phase 3 clinical trial against metformin [29]. In this study, dulaglutide

demonstrated no detriment and indeed showed within-group improvement from baseline in treatment satisfaction. This positive finding suggests that patients on average value the observed improvements in clinical outcomes more than the disutility of adding an injection. However, due to the blinded design of the study, potential benefits or detriments of differing modes and frequencies of administration cannot be identified by the patient. The observed lack of difference between groups does not diminish from the relevance or importance of this PROM endpoint; treatment satisfaction in a clinical trial is considered as a partial proxy for adherence to therapy in clinical practice [30,31] and may be associated with improved health status [32-34] and reduced healthcare cost [35-37]. Treatment satisfaction was also measured in another dulaglutide Phase 3 clinical trial, this time in an open-label design against exenatide [38]. In this study, dulaglutide demonstrated an improvement compared to baseline, and due to the study design it is sensible to look at between-group differences. The observed improvement was greater with dulaglutide than with exenatide.

Conclusion

Treatment of T2DM requires a progressive and multi-factorial treatment approach that addresses clinical and psychosocial aspects of living with diabetes. With careful consideration, appropriate PROM measures can be selected and truly robust assessments undertaken successfully in clinical research [22]. This article provides a proposed order for reading and interpreting PROM endpoints; absence of PROM detriment with the experimental therapy, improvement of PROM score with the experimental therapy, and where study design and prior analyses support it, a comparison of change in PROM scores between the experimental and control therapies. Taken together, efficacy, safety and PROM data from trials of experimental therapy can assist in providing care that is in line with patient values, per the principles of evidence-based medicine. This in turn may increase adherence in clinical practice.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	MR	CG
Research concept and design	--	--
Collection and/or assembly of data	--	--
Data analysis and interpretation	--	--
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