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Patient-reported outcome measures (PROMs) as proof of treatment efficacy

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Introduction

In recent years, patient-reported outcome measures (PROMs) have become increasingly popular in clinical practice and clinical trials. In this paper, we highlight the need for introducing measures to control for the bias associated with these inherently subjective measures and combining PROMs with objective outcomes, which do not depend on judgement, experience or performance.

PROMs measure the subjective elements of patients' conditions, including health-related quality of life, pain intensity, activity limitations, participation restrictions, satisfaction or adherence to treatment and help to evaluate the burden of disease and treatment from patients' perspectives.[1]

Originally, PROMs were used in pharmacological research to assess treatment effects in conditions such as cancer, in cases where the cure was not possible, and quality of life became the primary concern.[2] In the last 20 years, the use of PROMs has increased considerably,[1 3] and, currently, those outcomes are used to assess the effects of treatment and quality of care[2] and to evaluate policies[3] and to inform health economics.[4] One of the factors that contributed to the popularity of PROMs was their recognition by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a measure of treatment efficacy.[1 5 6] The FDA and the EMA define PROMs as any outcomes related to the patient's health or treatment that is evaluated directly by the patient, without any interpretation by a doctor or anyone else.[1 6] According to this definition, and in contrast to common perception, these outcomes do not necessarily measure what is the most important to patients or health itself.[7 8]

The role of PROMs

The main role of PROMs is that they provide important indicators of treatment efficacy not captured by objective markers or clinical assessments.[1 6] They may be used as 'red flags' during the assessment of acute symptoms and help to monitor response to treatment, for example, the efficacy of analgesia, especially if they are collected in real time.[2]

Moreover, well-developed PROMs for a specific condition may measure treatment effects on many domains, which is useful because treatment may have a different effect on disease-specific outcomes, health status and quality of life.[9] Finally, reporting PROMs improves communication between the patient and the care provider and, in turn, increases patient's satisfaction with treatment[2] and, subsequently, helps with adherence to the treatment itself and with patient retention.[10]

Considerations for the use of PROMs

Potential limitations and biases associated with PROMs are rarely acknowledged,[2 3 5 11] although both EMA and FDA recognise that PROMs may not be suitable as primary outcomes in open-label settings and that they should be supported by objective or functional outcomes.[1 6] By the nature of being subjective, PROMs may be affected by internal factors, such as mood, expectations, time and sentiments, and external factors such as treatment context, interactions with the healthcare providers and patients' socioeconomic situation, which leads to fluctuations in the outcomes. In trials, in which only patients with particularly severe symptoms and disability are recruited, this variability is higher, and PROMs' fluctuations associated with natural regression to the mean might be interpreted as a treatment effect.[12] Regression towards the mean after a different period of time from the end of each intervention might inflate type 1 error. However, some interventions take longer to work, and their effects may become apparent only after some time causing type 2 error.

Apart from being subjective, some PROMs also require patients to make a judgement regarding the treatment effects. Patients often overestimate benefits and underestimate the risks of treatments.[13] Under prospect theory, the value is assigned to gains and losses rather than to final assets, and those values depend on experience. This has profound implications for comparison of the efficacy, especially if one treatment arm is associated with an initial deterioration in function, for example, an operation or chemotherapy, followed by a fairly steady recovery, and can provide an overall perception of significant gain, known as the 'rebound' effect (figure 1). Moreover, patients are not necessarily able to identify an improvement in their own health. For example, the improvement measured using the maximum forced expiratory volume in 1 s in patients with asthma may not translate into a positive change in terms of patient-reported improvements when compared with placebo.[14] Therefore, it is important to combine PROMs with functional outcomes in order to gain insight into both physiological effect and patients' well-being. Similarly, what patients report as important may not be what they

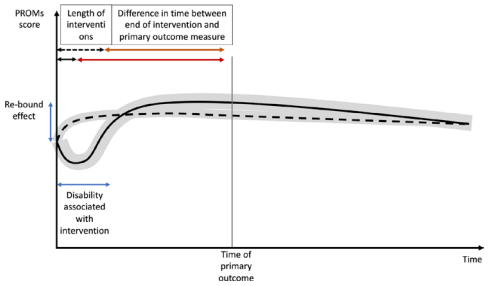

Figure 1 Change in PROMs with time and the 'rebound' effect. PROMs, patient-reported outcome measures.

actually choose. For example, patients often say that pain relief is the most important for them, but many do not take some of their pain killers and are willing to accept some level of pain in order to be able to function and they do not actually expect to be pain free.[15] These examples demonstrate that the assessment of treatment efficacy requires careful and multidimensional approach based on PROMs and functional outcome measures.

PROMs may be able to capture multiple domains, but the drawback of using PROMs with a broad outcome set is the tendency for patients to report only some of them. Selective reporting is a common problem despite reporting guidelines and clinical trial registries.[16] However, a narrow set of outcomes increases the risk of missing clinically meaningful changes. Finally, due to variability, PROMs measurements are often categorised, which reduces reliability and decreases power.[17]

Strategies to improve the use of PROMs

In open-label settings, patients are likely to exaggerate the treatment effect, especially if the treatment is invasive.[18 18 19] Blinding of patients reduces reporting bias as well as a risk of unbalanced attrition or cointerventions,[18] and blinding of doctors or researches reduces observer's and detection bias; however, biases related to unblinded patients tend to be larger than those caused by unblinded assessors.[19 20] When blinding is not possible, PROMs collection should be combined with functional, imaging and biochemical biomarkers adding an element of objectivity.[1 6]

The treatment effect should improve patients' satisfaction and surpass the placebo effect; therefore, when it is important to assess the magnitude of improvement or harms associated with an active intervention, a placebo-controlled randomised controlled trial (RCT) may be necessary.[21]

The variability of PROMs can be mitigated by collecting measurements at multiple time points to assess the trajectories of symptoms' progression and recovery. This approach has several benefits: it reduces the bias caused by the patient having a 'bad day', provides information about disease trajectories and treatment effects over time and helps to identify participants with similar patterns.[22]

Conclusions

PROMs provide evidence on the effect of interventions on patient symptoms and quality of life, but by the nature of being subjective, they are prone to bias. Blinded RCTs, preferably with a placebo control, are crucial if the evidence of efficacy is to be based on PROMs. Furthermore, collecting multiple PROMS over time as "progression trajectories" may help to overcome the single measure variability. Finally, PROMs should be used in conjunction with objective outcomes, especially when assessment by blinded clinicians or researchers is not possible.

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