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The Emerging Role of Patient-Reported Outcomes (PROs) in Clinical Trials in India

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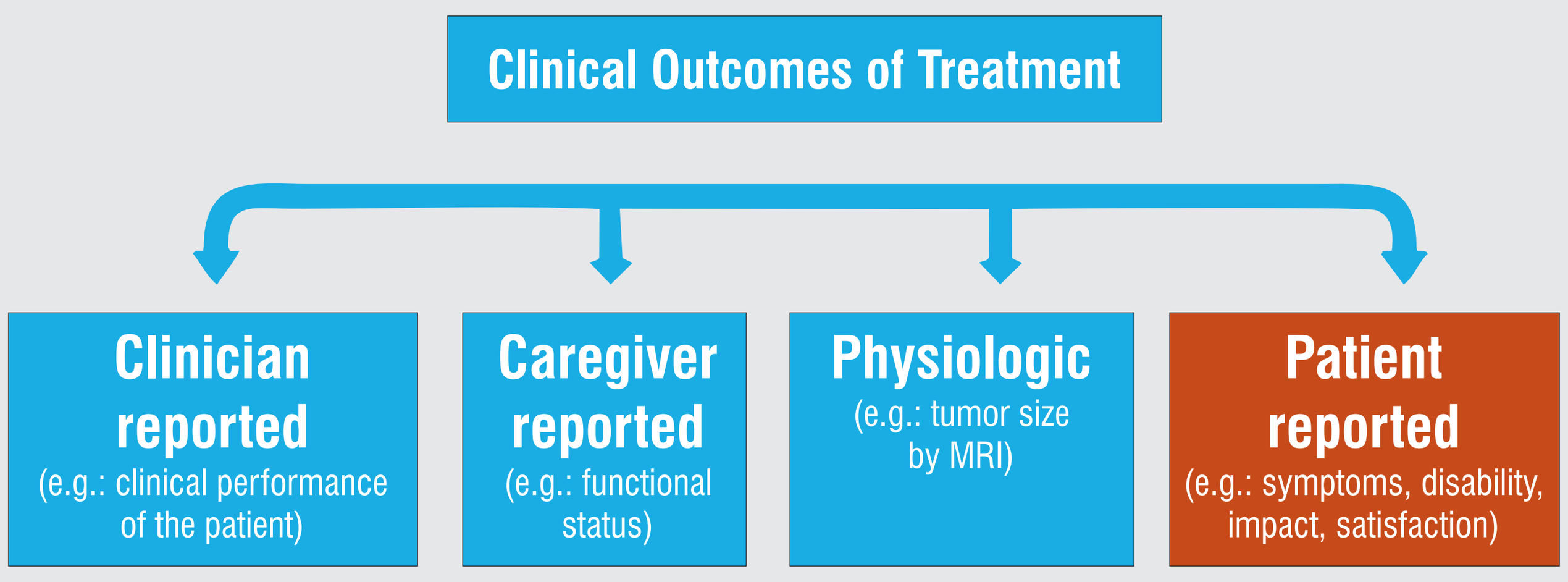
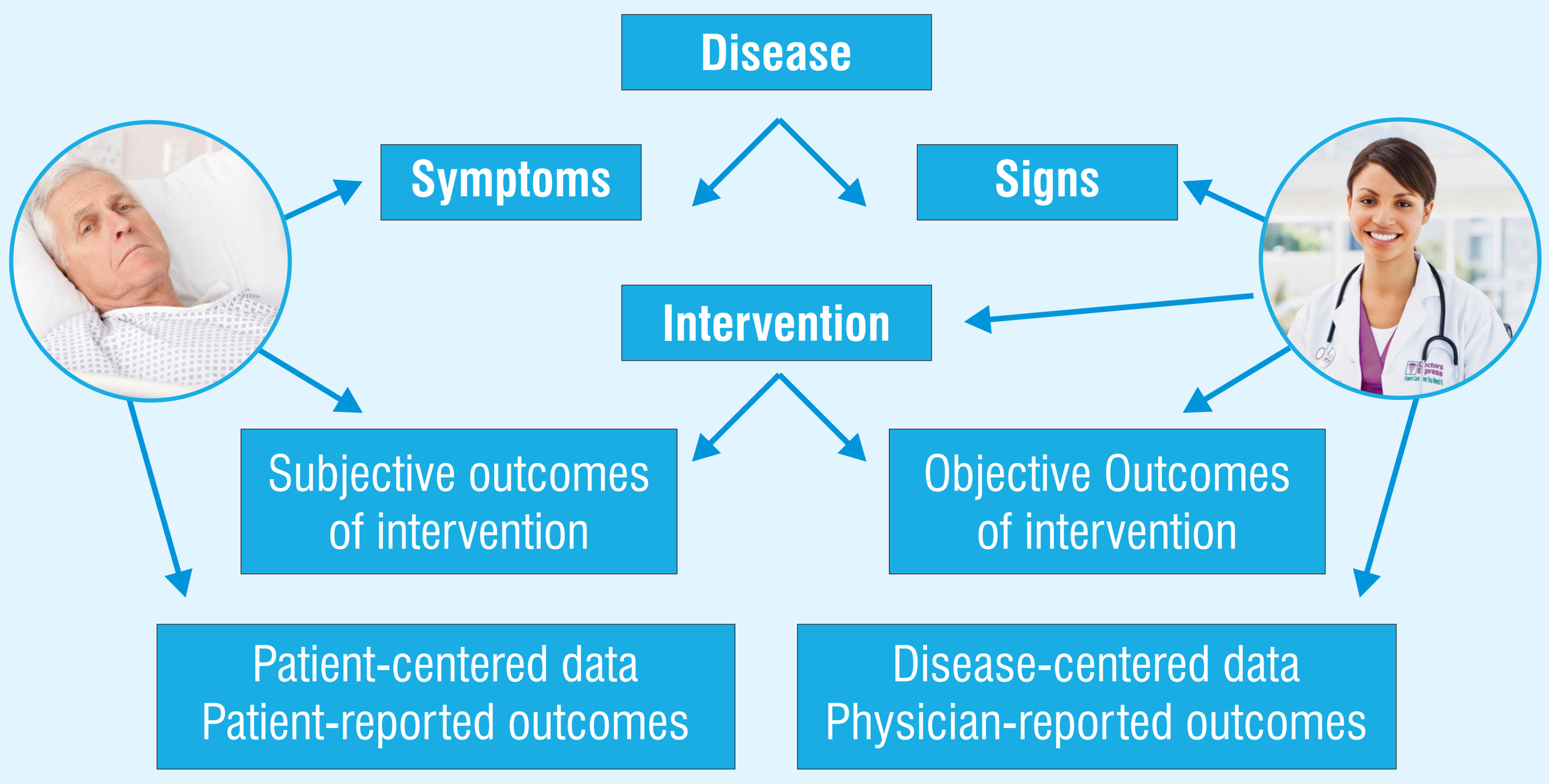
What are Patient Reported Outcomes (PROs)?

USFDA: A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. [1]

Types of Clinical Outcomes to a Treatment [2]



Why are PROs important?[3]



- Traditionally healthcare decisions are based on disease-centered data that is almost always doctor-reported
- This system focuses on the effect of an intervention on the patient's objective indicators rather than the subjective feeling of improvement: lacuna
- This lacuna can be overcome by supplementing with patient-centered data which are patient-reported
- PROs include:
  - Satisfaction scores
  - Symptom relief
  - Well-being
  - Productivity assessment
  - Intervention-induced problems

  Broader knowledge of the impact of an intervention
- PRO data are especially important in chronic, disabling conditions where improvement in patient suffering forms the most important aspect of therapy
- PRO data may be used: [4]
  - To inform clinical care and therapeutic decision making
  - To take reimbursement decisions
  - To predict long-term outcomes
  - To Influence health policy

PROs in Clinical Trials[4]

1. In many clinical trials, PROs are among the primary (rather than secondary) effectiveness endpoints
2. PROs are required to be shown in CTs by pharmaceutical companies in order to validate their label claims

PROs in Clinical Trials: Effectiveness Endpoints [4]

- PROs, including health-related quality of life (HRQoL), symptoms such as pain or fatigue, and health utility, are increasingly assessed in clinical trials as a measure of effectiveness
- Especially in clinical trials which evaluate conditions such as irritable bowel syndrome, migraine, pain, insomnia, asthma, psychiatric disorders, oncology etc
- However, the quality of PRO data can suffer in many trials because of high rates of missing data and inconsistencies in data collection
- This adversely affects the integrity and usefulness of such data in clinical practice.
- Despite the importance of PROs, studies suggest that protocols provide little guidance regarding PRO aspects of the trial
- This leads to ambiguity and significant inconsistency in PRO data collection, analysis and reports
- To improve optimal PRO data collection, study protocol should be equipped with adequate PRO items including specific instructions about PRO data collection

PROs in Clinical Trials: Validate Label Claims

> **Guidance for Industry**
> **Patient-Reported Outcome Measures: Use in Medical Product Development to support Labeling Claims**
>
> U.S. Department of Health and Human Services
> Food and Drug Administration
> Center for Drug Evaluation and Research (CDER)
> Center for Biologics Evaluation and Research (CBER)
> Center for Devices and Radiological Health (CDRH)
> December 2009 Clinical / Medical

- Inclusion of PROs in clinical trials provide valuable subjective information about a health intervention
- To capture this valuable data, many pharmaceutical industries have started to include PROs routinely in their clinical trials to validate the claims of their pharmaceutical products
- USFDA issued guidance documents for industry in 2006 (updated 2009) to be followed while developing PRO instruments for supporting label claims

PROs in clinical trials in India

- Clinical trials in India have started to use PROs as primary outcome measures
- Indian researchers have started to realise the importance of PROs in improving the validity of their findings

> Urology. 2014 May;83(5):1016-22. doi: 10.1016/j.urology.2013.12.026. Epub 2014 Feb 21.
>
> **Retrograde intrarenal surgery vs extracorporeal shock wave lithotripsy for intermediate size inferior pole calculi: a prospective assessment of objective and subjective outcomes.**
>
> Singh BP[1], Prakash J[2], Sankhwar SN1, Dhakad U[3], Sankhwar PL[4], Goel A[1], Kumar M1
>
> **Abstract**
>
> **OBJECTIVE:** To assess objective and subjective outcomes of retrograde intrarenal surgery (RIRS) and extracorporeal shock wave lithotripsy (SWL) for the treatment of intermediate size (1-2 cm) inferior calyceal (IC) stones in a prospective randomized fashion.
>
> **METHODS:** Between March 2011 and January 2013, 70 symptomatic adults who had isolated IC stone between 10 and 20 mm underwent RIRS or SWL by computer-generated pseudorandom assignment (1:1). Success rate, mean procedure time, hospital stay, pain score on day 1 and 2 using visual analog scale, analgesic requirement after discharge, complications, retreatment rate, auxiliary procedure, and patient-reported outcomes (using self-made nonvalidated questionnaire) were compared.
>
> **RESULTS:** Baseline parameters and mean stone size (SWL 16.45 ± 2.28 mm, RIRS 15.05 ± 3.56 mm; P = .0542) were comparable. Success rate was significantly higher after a single session of RIRS compared with 3 sessions of SWL (85% vs 54%; P = .008). Retreatment rate (65% vs 5.7%; P = .0001) and auxiliary procedure (45% vs 8%; P = .0009) were significantly higher in SWL. Pain score on postoperative day 1 and 2 was significantly higher in RIRS, but patients with SWL required significantly more analgesics afterward. Most of the complications were of Clavien grade I and/or II in both groups. Average time to return to normal activity and voiding symptoms were significantly higher in RIRS. Overall satisfaction score (2.17 ± 1.24 vs 2.82 ± 1.17; P = .026) was significantly higher in RIRS than SWL.
>
> **CONCLUSION:** For the treatment of intermediate size IC calculi, RIRS is superior to SWL in terms of objective and subjective outcomes.

> J Assoc Physicians India. 2013 Jan;61(1 Suppl):31-40.
>
> **Insulin analogue therapy improves quality of life in patients with type 2 diabetes in India: the A1chieve study.**
>
> Moses A[1], Chawla R[2], John M[3].
>
> Author information
>
> **Abstract**
>
> **AIMS:** To determine the effects on quality of life after starting insulin with, or switching to, insulin analogue therapies in Indians with type 2 diabetes mellitus in the 24-week, prospective, observational A1chieve study.
>
> **METHODS:** Health-related quality of life (HRQoL) was assessed at baseline and at 24 weeks by the validated EQ-5D questionnaire (visual analogue score [VAS] and five dimensions) in 20,554 people who had started using basal insulin detemir, mealtime insulin aspart (with or without a basal insulin) or biphasic insulin aspart 30.
>
> **RESULTS:** Quality of life improved in both insulin-naive and insulin experienced patients in all treatment groups. At the start of the study, 63.2% of the insulin-naive patients reported problems with walking but after 24 weeks, only 15.2% reported difficulties. At baseline all HrQOL parameters were deteriorated in Indian cohort and the improvement observed was highly significant and well appreciated. The improvement was seen across all insulin regimen and all regions around India.
>
> **CONCLUSION:** Compared with baseline scores, HRQoL improvement was seen after 24 weeks of treatment with all insulin analogue therapies

> Am J Gastroenterol. 2011 Feb;106(2):307-16. doi: 10.1038/ajg.2010.455. Epub 2010 Dec 14.
>
> **Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy (the RIME Trial).**
>
> Sidhu SS[1], Goyal O, Mishra BP, Sood A, Chhina RS, Soni RK.
>
> **Abstract**
>
> **OBJECTIVES:** Cirrhotics with minimal hepatic encephalopathy (MHE) have a poor health-related quality of life (HRQOL). Treatment of MHE is still evolving. The aim of this double-blind randomized pilot study was to assess the efficacy of rifaximin in improving neuropsychometric (NP) test performance and HRQOL in patients with MHE.
>
> **METHODS:** MHE was diagnosed if any two NP tests (number and figure connection tests, picture completion, digit symbol, and block design tests) were deranged beyond 2 s.d. of normal. HRQOL was assessed using the sickness impact profile (SIP) questionnaire.
>
> **RESULTS:** A total of 486 patients with cirrhosis were screened and 284 were found eligible. Out of these 115 (40.9%) had MHE, of which 21 refused consent and 94 were randomized to receive placebo (n=45) and rifaximin (n=49; 1200 mg/day) for 8 weeks. At the end of treatment, significantly more number of patients in rifaximin group showed reversal of MHE (75.5% (37/49) vs. 20% (9/45) in placebo group; P<0.0001). Rifaximin group also showed significant reduction in mean number of abnormal NP tests (baseline, 2.35 (95% confidence interval (CI), 2.17-2.53); 2 weeks, 1.29 (95% CI, 1.02-1.56), P=0.002; 8 weeks, 0.81 (95% CI, 0.61-1.02), P=0.000), compared with placebo group (baseline, 2.31 (95% CI, 2.03-2.59); 2 weeks, 2.03 (95% CI, 1.74-2.31); 8 weeks, 1.97 (95% CI, 1.69-2.25), P>0.05). The mean total SIP score also improved significantly in rifaximin group (baseline, 11.67 (95% CI, 10.31-13.03); 8 weeks, 6.45 (95% CI, 5.59-7.30); P=0.000) compared with placebo group (baseline, 9.86 (95% CI, 8.66-11.06); 8 weeks, 8.51 (95% CI, 7.35-9.67); P=0.82). Improvement in HRQOL correlated with improvement in NP tests. Rifaximin was well tolerated.
>
> **CONCLUSIONS:** Rifaximin significantly improves both cognitive functions and HRQOL in patients with MHE.

> Surg Endosc. 2011 May;25(5):1535-40. doi: 10.1007/s00464-010-1431-1. Epub 2010 Oct 26.
>
> **Do dietary spices impair the patient-reported outcomes for stapled hemorrhoidopexy? A randomized controlled study.**
>
> Agarwal Bb[1].
>
> **Abstract**
>
> **BACKGROUND:** Postoperative pain is a concern for patients seeking hemorrhoid surgery. Stapled hemorrhoidopexy is popular due to better patient-reported outcomes (PROs). Pain is the index of PROs. Posthemorrhoidectomy patients usually opt for a spice-free diet due to fear of pain or anal pruritus induced by spices. Curcumin and peprin (spice constituents) have powerful antiinflammatory and antioxidant properties. Ability to resume a normal taste-habituated meal may improve PRO quality of life. Thus, spice-related paradoxic conservatism in stapled hemorrhoidopexy, which involves no open wound, needed to be studied.
>
> **METHODS:** A prospective open-ended study (July 2008 to August 2009) investigated consecutive candidates for day-care stapled hemorrhoidopexy randomized by the date of birth method into a controlled group (receiving a spices-free diet) and a study group (receiving a spicy diet) after an ethics and informed consent protocol. A standard perioperative protocol was followed. At discharge, the patients were advised to resume a normal diet (spicy or bland) and instructed to maintain a pain diary (100-point visual analog scale [VAS]) and an analgesic diary. Paracetamol 650 mg was used for pain exceeding a VAS score of 25. Patients were followed on day 3 and weeks 1 and 3. Failure to be discharged from day care, failure to maintain patient diary, and squamous epithelium in the rectal donut were the withdrawal criteria.
>
> **RESULTS:** A total of 67 patients were randomized. The groups were well matched for demographics, comorbidities, types of anesthesia, hemorrhoidal grades, and withdrawal. Statistically significant improvement in PROs (P<0.05) and a lower consumption of analgesic tablets were seen in the study group (spicy diet). No adverse event was reported in either group.
>
> **CONCLUSION:** Resumption of a spicy diet has no adverse impact on PROs after stapled hemorrhoidopexy. Reduced analgesic usage in the spicy diet study group needs to be evaluated further for any potential benefits of spices.

- However, there is no proper guidelines for conducting proper patient-centered outcome research (PCOR) in India
- DCGI (Drugs Controller General of India) has not given any guidelines similar to the USFDA regarding using PRO measures to validate label claims
- Potential role of routinely using PROs in Indian Cts:
  - Determination of patient eligibility
  - Determination of patient compliance
  - As a study endpoint
  - Determination of health-related quality of life (HRQoL) following intervention
  - Assessing economic burden and indirect impact of disease and treatment
- Generic pharmaceutical market is strong and widespread in India
  - Implementation of PROs in CTs should be made mandatory for pharmaceutical companies to prove their label claims, especially for new generic products
  - India's population and healthcare needs are diverse
  - Uniform health-related policy decisions are not always rational and implementable throughout the country
  - Data obtained from PROs in CTs should be made the source document for making health-related decisions at all levels in India
- Implementation of regular PROs assessment in clinical trials can help in:
  - Determining the negative effects of therapy
  - Comparing different standard therapies having similar survival outcomes
  - Finding out whether a new therapy is preferable to standard therapy
  - Determining whether a therapeutic regimen is better than supportive care only, when survival time is short
  - Making the communication easier in clinical practice

CONCLUSIONS

- PROs in clinical trials have prominent roles, specially as effectiveness endpoints and to validate label claims
- Their role is even more prominent in India for evaluating indirect effects and economic burden of different therapies
- PRO data are required to make rational healthcare policy decisions in the backdrop of a diverse population
- A uniform guidance document, such as the one by USFDA, is not available in India to regulate PRO inclusion for label claim validation
- This lacuna is important in the backdrop of the generic-dominated pharmaceutical scenario in India

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2. Deshpande PR *et al. Perspect Clin Res* 2011;2:137-44
3. Dang A, Vallish BN. *Int J Med Public Health* 2015;5:125-7
4. Calvert M *et al. PLoS ONE* 2014;9(10):e110216

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