Use and Validity of Patient-Reported Outcomes in Schizophrenia Trials

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The Methodological Question Being Addressed

This study seeks to understand how often patient-reported outcomes (PROs) are used in Schizophrenia clinical trials and determine if they are consistent with results obtained from clinician-reported outcomes.

INTRODUCTION

The FDA has encouraged the use of PROs in clinical trials for many years to augment data from clinician-reported outcomes (ClinROs). PROs have been used to a lesser degree in trials with the severely mentally ill populations due to concerns about deficits in general cognition and insight. We believe that evaluation of the patient's perspective and experience with regard to quality of life, symptom status and healthcare utilization is crucial in Schizophrenia for ascertaining the full picture of treatment efficacy.

In this study we reviewed the frequency of PRO instrument use in a sample of Schizophrenia trials and analysed correlations between two clinician-administered scales commonly seen as gold standards in Schizophrenia trials - the Personal and Social Performance Scale (PSP) and the Positive and Negative Syndrome Scale (PANSS) - and the Quality of Life (QOL) measure EQ-5D-5L, a PRO scale routinely used for health-economic modelling.

METHODS

We performed a search of 15 recent acute Schizophrenia studies. A total of 652 baseline visits in two acute clinical trials and 7 countries in North America and Eastern Europe were analysed. Spearman correlations were calculated between 1) EQ-5D-5L dimensions and PSP totals, 2) EQ-5D-5L VAS scores and PSP totals, 3) EQ-5D-5L dimensions and 4) EQ-5D-5L VAS scores and PANSS total scores. Level of significance was set at $p < 0.05$.

Populations:

PANSS positive symptom score (mean): 26.2

PANSS negative symptom score (mean): 24.7

PSP (mean): 46.9

RESULTS

In the 15 schizophrenia trials we reviewed, only 2 trials were identified as having used the EQ-5D-5L to evaluate QoL, while the 2 other studies used PROs that were symptom-specific.

Figure 1. Spearman Correlations between EQ-5D dimensions and PANSS, PSP

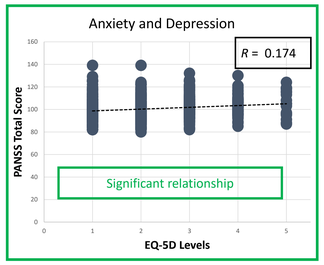
EQ-5D-5L to PANSS Correlations: Spearman's correlations ranged from 0.042 to 0.174 for the EQ-5D-5L dimensions. Three EQ-5D-5L dimensions - anxiety and depression, self-care, and pain and discomfort - demonstrated significant relationships with PANSS total score ($p < 0.05$), whereas the others EQ-5D-5L dimensions did not.

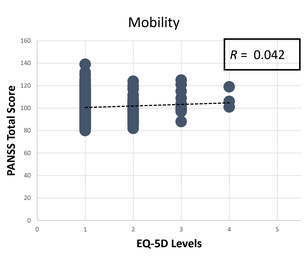
EQ-5D-5L to PSP Correlations: Spearman's correlations between PSP total and the EQ-5D-5L dimensions anxiety and depression, mobility, pain and discomfort, and usual activities were nonsignificant, ranging from r = -0.122 to -0.021. Of note, only the EQ-5D-5L domain of self-care yielded significant relationships ($p < 0.05$).

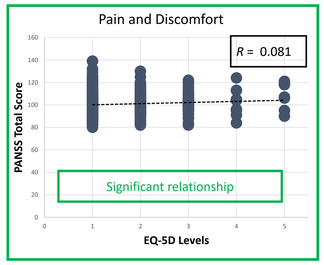
The EQ-5D VAS score demonstrated non-significant correlations with both PSP total (r=0.046) and PANSS total (r = - 0.066).

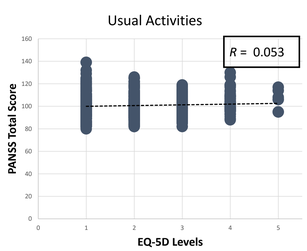
EQ-5D dimensions: **1** – no problem, **2** – slight problem, **3** – moderate problem, **4** - severe problem, **5** – extreme problem or unable to perform

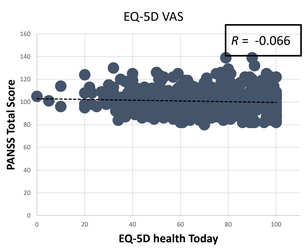
PANSS





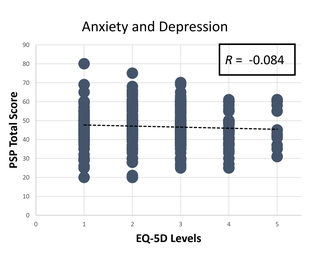


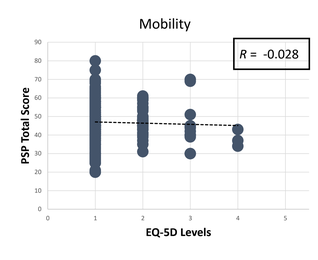


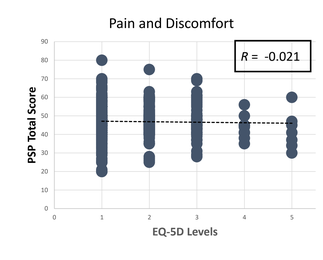


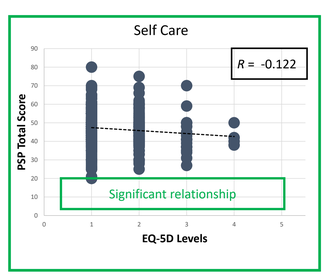
The significant relationship of PANSS total score and with the EQ-5D-5L domain of anxiety and depression dimension highlights patient's ability to voice distress, despite potential the lack of insight associated with more severe PANSS scores. Difficulties with self-care have been widely reported in the Schizophrenia population [1]. More severe pain/ and discomfort associated with higher PANSS scores may stem from acute delusions, or genuine physical and medical comorbidities known to be associated with Schizophrenia [1].

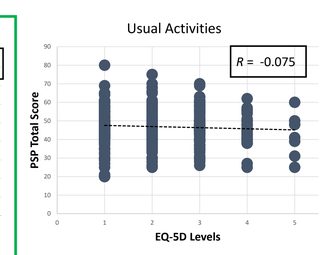
PSP

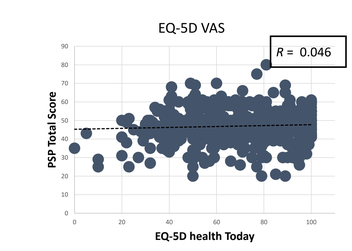












On the PSP the only significant, but negative, relationship was discovered with the self care dimension suggesting the most severe patients may be unable to assess this, domain while less severe patients are able to report their functioning well.

CONCLUSIONS

The appropriateness of the EQ-5D-5L for people with schizophrenia has both been supported and contested [4, 5, 6, 8]. Here, we demonstrate that the use of the EQ-5D-5L is uncommon in Schizophrenia trials, and most dimensions and VAS scores show no statistically significant relationship with two of the gold standard instruments used in Schizophrenia trials, the PSP and the PANSS, potentially driven by the EQ-5D's focus on **physical functioning** rather than mental health.

This study highlights the need to select QOL PROs for use in Schizophrenia trials carefully to add the patient's voice and their quality of life to the investigational product efficacy evaluation process as well as health-economic modelling.

This study is limited in terms of its use of data from an acute population. It is possible that stronger correlations would be seen in studies of a stable population with more insight. Additional considerations to measure QOL in this indication may include:

- Use of EQ-5D Proxy (1) version designed for cases where patients are unable to self report due to mental illness
- Use of health care resource utilization questionnaires as a proxy for investigating QoL
- Use of other PROs such as the Heinrichs-Carpenter Quality of Life Scale (QLS) short version (7 items) that correlates well with severity of Schizophrenia [2, 3]
- For health economic modeling, consider utilizing discrete choice experiments instead of pure EQ-5D utility score [7]
- Differentiated use or analysis of PROs by level of insights and cognition; consider inclusion of caregiver impact questionnaires (e.g., Zarit Burden Interview)

Further analysis will aid our understanding of QOL reported by people with Schizophrenia, including:

- Subgroup analysis by PANSS Marder factors to understand QOL relationships with different PANSS domains
- Role of cognition and level of insight to understand the relationship to the PRO
- Sensitivity to change analysis: Is the EQ-5D's sensitivity to change consistent with that of clinician-administered scales

References

[1] Nordstroem et al., 2017
[2] Bilker et al., 2002
[3] Fervaha et al., 2014
[4] Pitkaenen et al., 2011
[5] McGabe et al., 2018
[6] Millier et al., 2014
[7] Tinelli et al.,2016
[8] Purba et al., 2021

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