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Quality of life across domains among individuals with treatment-resistant depression

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Abstract

Background: Treatment-resistant depression affects millions of people worldwide and is a leading cause of disability and suicide. Studies of treatment-resistant depression outcomes have traditionally focused on depressive symptoms and functional impairment. Quality of life (QoL) has not been well described. We aimed to measure QoL in individuals with treatment-resistant depression and to determine how QoL was related to traditional measures of symptoms and social functioning.

Methods: We used a reliable, cross-culturally validated questionnaire, the abbreviated World Health Organization Quality of Life scale (WHOQOL-BREF), to prospectively measure QoL in 79 patients with treatment-resistant depression who were referred for electroconvulsive therapy at a United States tertiary-care medical center. QoL was characterized in four domains: physical, psychological, social, and environmental. QoL domains were examined for association with demographic variables, patient-reported depressive symptoms, functional impairment, and childhood adversity, as well as clinician-rated scales.

Results: Relative to published international norms, mean QoL scores were low in physical (standardized score, $z = -2.0$), psychological ($z = -2.6$), and social ($z = -1.0$) domains, but not in the environmental domain ($z = 0.2$). After controlling for age and income, patient-rated depressive symptoms correlated with physical (Pearson correlation, $r = -0.26$) and psychological ($r = -0.43$) QoL, whereas adverse childhood experiences correlated with environmental QoL ($r = -0.33$). Patient-rated functional impairment correlated modestly with all domains ($r = -0.25$ to -0.39). Surprisingly, QoL correlated very weakly with clinician-rated measures. These modest associations of QoL with other clinical scales were confirmed in multiple regression analyses.

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⁶.Disclosure Statement

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⁸.Supplementary Material

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Limitations: We used a single QoL instrument, which did not allow us to directly compare the WHOQOL-BREF scale with other commonly used instruments. Our sample was recruited from a single academic medical center in the Midwest region of the United States and was largely Caucasian. These factors may limit generalizability to other settings and ethnicities.

Conclusion: Among individuals with treatment-resistant depression, QoL is lowest in the psychological and physical domains. QoL is only modestly correlated with patient-rated symptoms and functioning, and even more weakly correlated with clinician-rated scales, indicating that measures of symptoms and functioning cannot serve as QoL proxies. QoL should be assessed when caring for patients with treatment-resistant depression. When developing novel biological, psychological, and social interventions for treatment-resistant depression, QoL should be targeted as a distinct clinical outcome.

Keywords

Treatment-resistant depression; quality of life; functional impairment; childhood adversity; major depressive disorder; bipolar disorder

1. Introduction

Depression is a common, debilitating illness that often fails to respond to first- and second-line treatments. For example, about one-third of patients did not reach remission after multiple optimized pharmacologic trials during the STAR-D study (Rush et al., 2006). Recent estimates for treatment resistant depression (TRD), often defined by two or more treatment failures, indicate a 12-month prevalence rate of approximately 2% in the US (Nemeroff, 2007). Furthermore, long-term outcomes of TRD are typically very poor. For example, chronic TRD has been associated with poor social function, persistent symptoms, increased mortality, and a recovery rate of less than 40% over 10 years (Fekadu, Wooderson, Markopoulou, et al., 2009; Fekadu, Wooderson, Markopoulou, & Cleare, 2009). TRD is increasingly recognized as a disease worthy of study in its own right, but the optimal methods of assessment of TRD have yet to be defined (Conway, George, & Sackeim, 2017; McIntyre et al., 2014).

Quality of life (QoL) is a broad construct encompassing multiple aspects of well-being, including physical, psychological, social, and environmental components. QoL differs from other commonly-used outcome measures such as depressive symptoms and social and occupational functioning. Assessment of QoL includes questions about symptom severity and daily functioning, but beyond that it also covers subjective well-being across multiple dimensions. Because a patient's overall condition results from a complex interplay between these different dimensions, focusing only on function and symptoms may fail to improve subjective QoL. Consequently, measuring QoL has been proposed as an essential component for clinical trials in mental illness as the assessment takes into account patients' rights, autonomy, and opinions (Mas-Expósito, Amador-Campos, Gómez-Benito, & Lalucat-Jo, 2011; Oliveira, Carvalho, & Esteves, 2016; Barneveld, Swaab, Fagel, van Engeland, & de Sonnevile, 2014; Rubio et al., 2014). There is a need for simultaneous use of multiple assessment tools -- including objective evaluations via quantitative questionnaires of functioning, symptoms and measures of subjective QoL -- in order to obtain a more

complete clinical picture across physical, psychological, social, and environmental domains and to understand the determinants of QoL in clinical populations (Caldirola et al., 2014; Karow, Wittmann, Schöttle, Schäfer, & Lambert, 2014).

Previous studies have measured QoL among patients with depression, including the narrower phenotype of TRD. In a systematic review, Ishak and colleagues summarized QoL impairments in depressive disorders and QoL improvements associated with successful treatment (Ishak et al., 2011). The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) developed by Endicott and colleagues, a sensitive measure of satisfaction and well-being across various areas of daily functioning (J. Endicott, Nee, Harrison, & Blumenthal, 1993), has proven useful for measuring QoL among patients with major psychiatric disorders (Ritsner, Kurs, Gibel, Ratner, & Endicott, 2005). Notably, across a spectrum of anxiety and depressive disorders, symptom measures were shown to explain only a small proportion of the variance in the Q-LES-Q, suggesting that QoL cannot be assessed by measuring symptoms alone (Rapaport, Clary, Fayyad, & Endicott, 2005). Consistent with this finding, individuals with sub-syndromal depressive symptoms reported impairment in well-being that was similar to that of fully symptomatic major depression (Judd, Paulus, Wells, & Rapaport, 1996). Within the specific condition of TRD, Rosenquist et al. reviewed studies of health-related QoL and highlighted the profound effects that TRD has on physical, psychological, and social functioning, as well as life satisfaction and well-being (Rosenquist, Brenes, Arnold, Kimball, & McCall, 2006). Most previous studies of QoL among patients with TRD have used the 36-Item Short Form Health Survey (SF-36) (McCall et al., 2011; Qiao, Qian, Zhao, Gong, & Geng, 2017; Solvason et al., 2014). The SF-36 has the favorable qualities of multi-domain assessment and availability of normative data. However, it has not been widely validated or normed across languages and cultures. The SF-36 also measures a somewhat narrower construct, health-related QoL, that is limited to the effects of diseases and treatments on QoL.

The abbreviated World Health Organization Quality of Life Questionnaire (WHOQOL-BREF) is a 26-item, 4-domain scale developed by the World Health Organization to measure QoL in the physical, psychological, social, and environmental domains. The WHOQOL-BREF scale has become the most widely used multidimensional QoL measure in international health research (Kenneth C. Land, Alex C. Michalos, & M. Joseph Sirgy, 2011, p. 414) because it is cross-culturally validated and available in most of the world's major languages (Skevington, Lotfy, O'Connell, & WHOQOL Group, 2004). Furthermore, it is internationally normed for 23 countries all over the world. In addition, it measures the broader construct of global QoL, which is not specific to disease states (Huang, Wu, & Frangakis, 2006). In contrast to health-related QoL instruments, measures of global QoL may be more useful when developing rational policies for distribution of resources for health-related versus non-health-related problems. To our knowledge, just one brief report has used the WHOQOL-BREF to measure QoL among individuals with TRD (Antunes & Fleck, 2009). They investigated the effects of electroconvulsive therapy (ECT) on QoL of a heterogeneous sample of 58 psychiatric inpatients in Brazil, some of whom had TRD, and found improvements across QoL domains.

The current study had two objectives. The first objective was to measure physical, psychological, social, and environmental QoL among a well-characterized cohort of individuals with severe TRD using a multi-domain, validated, reliable, cross-cultural instrument (i.e., the WHOQOL-BREF). The second objective was to compare QoL domains to outcome measures of symptom severity and functional impairment commonly used in studies of TRD to determine whether the WHOQOL-BREF scale provides information beyond that measured by traditional scales. The rationale was that, because the construct of QoL includes subjective symptoms of depression and perceived functional abilities, it was possible that the WHOQOL-BREF scale would strongly correlate with scales that measure severity of symptoms and functional impairment. In that case, the WHOQOL-BREF scale would be redundant and traditional measures could be used as proxies for QoL. On the other hand, the WHOQOL-BREF scale may correlate only weakly with traditional outcomes, as shown with the Q-LES-Q scale across anxiety and affective disorders (Rapaport et al., 2005). If that is the case for TRD, then QoL could not be measured by proxy and would therefore need to be assessed independently.

2. Material and Methods

Study design

The Michigan Biomarkers for Refractory Depression (Bluebird) study was conducted at the University of Michigan, Ann Arbor, between 2011 and 2016. This prospective, longitudinal, observational study of TRD recruited inpatients and outpatients who were referred to the ECT Program at the University of Michigan. We focused on this patient population because it represents a relatively severe, inadequately studied subgroup of depressed patients who are high utilizers of health care resources. Here we focus on baseline clinical measures; biomarker findings and longitudinal follow-up data will be described elsewhere. The study was approved by the University of Michigan Institutional Review Board. All subjects provided written informed consent.

Recruitment and assessment

Eligible patients met the following criteria: 18 years old at the time of consent; clinical diagnosis of a moderate-to-severe depressive episode (DSM-IV/DSM-V major depressive disorder or bipolar disorder) for at least 2 months; medication resistance, defined as non-response to at least one adequate medication trial within the current episode; considering treatment with ECT; and capacity to provide informed consent. An adequate medication trial was defined by a score of at least 3 according to the Antidepressant Treatment History Form (ATHF; (Sackeim, 2001), reflecting a minimum of 4 weeks of treatment with at least one well-established antidepressant medication at a moderate-to-high dose (e.g., nortriptyline > 75 mg per day for 4 weeks). It is important to note that we distinguished medication resistance from intolerance (inability to complete an adequate medication trial). Exclusion criteria were: medically or psychiatrically unstable or requiring a higher level of care; a manic/mixed episode within the past 6 months, or rapid cycling within the past 12 months; ECT within the past year; primary psychotic disorder (e.g., schizoaffective disorder); secondary mood or psychotic disorder (e.g., due to a general medical condition or substance

use); dementia; delirium; personality disorder as a current focus of treatment. Each subject was paid \$20–40 for participating.

Each participant received two independent, comprehensive evaluations by board-certified psychiatrists. A chart review of those evaluations was used during screening and baseline assessments. To ensure that a full range of psychiatric comorbidities and depressive symptoms was assessed, subjects were also interviewed by a masters-level clinical psychologist who had more than two years of experience working with patients with severe mental illness. The interview incorporated the Mini International Neuropsychiatric Interview Plus, version 5.0.0 (Sheehan et al., 1998) and the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (J. Williams & Terman, 2003). Supplemental questions were administered to gather information about history of mood disorders in first-degree family members and about tobacco use. Based on clinical interviews and the chart review, the research psychologist and a research psychiatrist conferred to reach a consensus regarding diagnosis and clinical features for each participant. Medication resistance during the current episode was characterized using the Massachusetts General Hospital (MGH) staging method (Fava, 2003). The Maudsley staging method (Fekadu, Wooderson, Donaldson, et al., 2009) -- a multidimensional scale based on severity, episode duration, and medication resistance -- was also applied. For individuals with bipolar disorder, “antidepressant” trials included trials of mood-stabilizer or antipsychotic medications approved for bipolar depression.

Instruments

The WHOQOL-BREF is a self-report questionnaire (WHOQOL Group, 1998) that comprises 26 questions. The first question asks about overall QoL, rated from “very poor” (1) to “very good” (5). The second question asks about satisfaction with health, rated from “very dissatisfied” (1) to “very satisfied” (5). The remaining 24 specific questions assess four QoL domains: physical (7 items), psychological (6 items), social relationships (3 items), and environmental (8 items). The score for each domain ranges from 4 to 20; high values represent a high QoL. Some previous studies have used a transformed scale ranging from 0 to 100. To allow comparison with those studies, we reverse-transformed their mean scores (m) using the formula $0.16m + 4$ and standard deviations (s) using $0.16s$. Skevington and colleagues demonstrated good-to-excellent psychometric properties of the WHOQOL-BREF in a large sample of healthy individuals and those with physical and mental illnesses (Skevington et al., 2004). The reliability and validity of the WHOQOL-BREF has been investigated in other psychiatric populations (Berlim, Pavanello, Caldieraro, & Fleck, 2005; Carpinello, Pinna, Carta, & Orrù, 2006; Trompenaars, Masthoff, Van Heck, Hodiament, & De Vries, 2005).

Clinician-rated and patient-rated scales were used to measure symptom severity and functional impairment. Clinician-rated scales included the 17-item Hamilton Depression Rating Scale (HDRS), the Global Assessment of Functioning (GAF) scale, and the Clinical Global Impression Severity (CGI-S) scale. The HDRS has been shown to be a valid and reliable measure of symptoms among depressed individuals (Williams, 1988). The GAF scale measures a combination of social and occupational functioning and psychological

symptoms (Jones, Thornicroft, Coffey, & Dunn, 1995). Although this scale is well known internationally and widely used for scoring the severity of illness in psychiatry, its reliability and validity are limited (Aas, 2010). The CGI-S scale measures overall severity of mental illness (Busner & Targum, 2007). This scale has previously been used as a brief, valid, and user-friendly alternative for patients with depression and anxiety (Leon et al., 1993). Three patient-rated scales were used. The Patient Health Questionnaire (PHQ-9), which measures the severity of depressive symptoms is a reliable and valid measure of depression severity (Kroenke, Spitzer, & Williams, 2001). The Work and Social Adjustment Scale (WSAS), which rates the ability to work, pursue leisure activities, and maintain relationships (Mundt, Marks, Shear, & Greist, 2002), has high internal reliability and is sensitive to treatment effects (Zahra et al., 2014). The Adverse Childhood Experiences (ACE) scale includes a set of 10 dichotomous questions assessing abuse, neglect, and other adverse life events before the age of 18 (Dong et al., 2004). The ACE is a widely used instrument but we are aware of validation studies of this instrument.

Data Analysis

The data was analyzed using SPSS version 17.0. We compared our data with international published norms of the WHOQOL-BREF (Skevington et al., 2004) and calculated individual-subject z-scores using the published international mean and standard deviation. To examine associations of QoL scores with other variables, we first tested demographic variables that were associated with QoL. Associations of QoL with clinical measures were then calculated while controlling for important demographics (age and household income). Multiple linear regression analyses used the Stepwise method in SPSS with default criteria. All tests were two-tailed. Following convention, we describe Pearson correlations (r) with absolute values <0.3 as small/weak, 0.3 to <0.5 as medium/moderate, and 0.5 as large/strong (Landau & Everitt, 2003).

3. Results

Quality of life in treatment-resistant depression

Seventy-nine participants enrolled in the study and completed the WHOQOL-BREF questionnaire. Demographic and clinical features of the sample are shown in Table 1 and Supplemental Tables S1. WHOQOL-BREF scores are shown in Table 2. Eighty-one percent of participants rated their overall QoL as “poor” or “very poor.” Seventy percent reported being “dissatisfied” or “very dissatisfied” with their health. Distributions of standardized scores, based on international normative data (Skevington et al., 2004), are shown in Figure 1. On average, physical and psychological QoL scores were at least 2 standard deviations below the norm, social QoL scores were about 1 standard deviation below the norm, and environmental QoL scores were consistent with international norms.

Demographic associations with quality of life

We identified significant correlations of QoL domains with age and household income. Older adults reported higher levels of physical QoL ($r=0.25$, $p=0.03$, $N=79$) and psychological QoL ($r=0.37$, $p=0.001$, $N=78$). Persons with a higher income showed a higher social QoL ($r=0.373$, $p=0.001$, $N=75$) and environmental QoL ($r=0.34$, $p=0.003$, $N=76$).

Married participants reported higher QoL in the social domain, but this association was eliminated when controlling for age and household income ($F=0.925$, $df=9$, $p=0.51$). We found no significant associations with sex or education (all $p > 0.05$). Because age and household income were strongly related to QoL, we included these variables as covariates in subsequent analyses of clinical variables.

Quality of life versus traditional clinical measures

Values for clinician-and patient-rated measures of symptom severity and functional impairment and their inter-correlations are shown in Supplemental Tables S1 and S2.

Table 3 shows univariate associations between these clinical instruments and QoL domains. In general, patient-rated scales showed weak-to-moderate correlations with QoL domains, and clinician ratings of symptoms and function were only weakly correlated with QoL ratings.

Because multiple clinical scales were associated with QoL domains, we wondered which clinical measures were strong and independent predictors of QoL. To address that question, we performed multiple regression analyses (with QoL as the dependent variable) starting with the most prominent predictors from the univariate analyses described above: age, household income, PHQ-9, WSAS, ACE, and HDRS. As shown in Table 3, WSAS independently predicted physical and social QoL, whereas the PHQ-9 independently predicted psychological QoL. Interestingly, the ACE scale was the only independent predictor of environmental QoL. HDRS did not independently predict any QoL domain.

4. Discussion

This study aimed to (1) measure domain-specific QoL among individuals with TRD using a valid, cross-cultural instrument and (2) compare QoL measures with traditional measures used to assess individuals with TRD -- i.e., symptom severity and functional impairment. We found that mean QoL scores were very low in the physical and psychological domains, moderately low in the social domain, and slightly high in the environmental domain. Furthermore, we identified weak-to-moderate correlations of QoL with patient-rated social and occupational function and with patient-rated depressive symptoms. Surprisingly, there were no meaningful associations of QoL with clinician-rated scales.

In comparison to previous studies of neuropsychiatric disorders, our results for physical, psychological, and social QoL are among the lowest reported. In Table 5, we compare QoL in our sample to values reported previously from individuals with various diseases in a range of countries, health systems, and socioeconomic conditions. The WHOQOL-BREF enables these kinds of comparisons because it has been cross-culturally validated, translated into multiple languages, and internationally normed. Although low psychological QoL was expected, the very low physical QoL that we found might not be expected of a disease often perceived as "psychological." For example, our TRD patients rated their physical QoL similarly to a sample of patients with advanced Parkinson disease (Hirayama, Gobbi, Gobbi, & Stella, 2008). Among the studies in Table 5, the sample of mixed psychiatric inpatients treated with ECT in Brazil appeared the most similar to ours (Antunes & Fleck, 2009). Our

results confirm their findings of very low physical and psychological QoL, and low social QoL. Environmental QoL in our sample was normal or high, depending on the comparison. This is not surprising since our participants had access to health care, insurance, and the resources needed to obtain complex medical treatments. These kinds of QoL measurements may be informative for policy makers who aim to distribute resources in a way that optimizes QoL across a health care system, region, or country, or even internationally.

The second major finding of our study was the relatively weak correlation of QoL scores with other patient-and clinician-rated outcome measures. Associations of patient-rated measures of social and occupational function and depressive symptoms with QoL scores ranged from weak to moderate. The strongest such associations were between PHQ-9 scores and psychological QoL scores ($r = -0.43$) and between WSAS scores and physical QoL scores ($r = -0.39$); all other associations were weak (magnitude of $r < 0.3$). These findings indicate that less than 20% of the variance in QoL was explained by these patient-rated scales. These results are reminiscent of previous studies relating symptoms with QoL. For example, self-perceived psychopathology (e.g., depressive symptoms and paranoia) was found to be the strongest predictor of subjective QoL measured using the Lancashire Quality of Life Profile, but it explained only 27% of the variance in QoL (Lasalvia, Ruggeri, & Santolini, 2002). A study using the Q-LES-Q scale across a range of affective and anxiety disorders found that symptom scales explained no more than 26% of the variance in QoL (Rapaport et al., 2005). In our study, clinician-rated measures correlated even more weakly with QoL than patient-rated scales, and did not independently predict QoL ratings in any domain. This finding is consistent with the lack of congruence between patient and physician ratings that has previously been described (Suarez-Almazor, Conner-Spady, Kendall, Russell, & Skeith, 2001). The weak relationship between QoL scores and traditional clinical measures may be explained in part by the fact that symptoms and functioning represent only a subset of the facets that constitute QoL. As highlighted by Rapaport and colleagues, a variety of other factors are likely to contribute to perceived QoL, including personality traits, availability of social and financial support, and degree of life success (Rapaport et al., 2005). It is also possible that severe forms of depression involve disturbances in the (as yet unidentified) neural systems that generate a sense of well-being and satisfaction with life in a way that is partially independent of the generation of typically measured depressive symptoms. In general, the weak-to-moderate associations between QoL domain scores and other measures of function or symptoms indicate that those measures cannot serve as proxies for QoL. This suggests that in future TRD outcomes research, QoL instruments should be used in addition to measurements of function and symptoms, especially since the most commonly used outcome currently is the clinician-rated HDRS. Integration of QoL measures in TRD research is likely to broaden our understanding of TRD and amplify the impact of novel interventions for individuals with TRD.

The utility of QoL scales for tracking change over time is not well established for psychiatric disorders, but several studies have reported longitudinal measures using the WHOQOL-BREF. Mas-Exposito and colleagues (Mas-Expósito et al., 2011) showed almost the same QoL level in schizophrenia in a 1 year follow up after medical and psychological interventions. Studies of individuals with schizophrenia (Garg et al., 2011) and psychiatric inpatients with mixed diagnoses (Antunes & Fleck, 2009) showed improvement of QoL after

an ECT intervention in comparison to baseline. Berlim and colleagues (Berlim et al., 2005) reported improvements in QoL after medical intervention for major depression compared to baseline. It is important to note that the HDRS measures week-to-week changes in symptoms, while QoL is typically measured monthly. As a consequence, symptom scales and QoL scales may have different strengths in measuring change over time. To clarify these differences, future research should simultaneously measure symptoms and QoL longitudinally during and after treatment interventions.

Unexpectedly, ACE questionnaire score turned out to be negatively correlated with environmental QoL scores in our sample, and not correlated with other QoL measures. Not surprisingly, household income was also associated with environmental QoL score, but multiple regression showed that ACE score was an independent predictor beyond income. An association with psychological or physical QoL measures might be expected, given recent studies which have shown low health-related QoL among those who grew up with a mentally ill person in the family (Morris, Kouros, Fox, Rao, & Garber, 2014). Instead, we found a specific association between childhood adversity ratings and environmental QoL scores which, to our knowledge, has not previously been reported. We speculate that individuals in our sample who experienced adversity during childhood were more likely to live in low-quality, dangerous, or impoverished neighborhoods, and that those individuals were also more likely to live in such neighborhoods as adults. Future studies are warranted to more fully explain this finding.

Limitations:

This study is the first to our knowledge to use the WHOQOL-BREF scale in a well-characterized cohort of individuals with TRD. Consequently, an important limitation of this study is that this scale has not previously been validated in this population. Nonetheless, this scale has been shown to have adequate psychometric properties among similar psychiatric populations, which would support its use in persons with TRD (Berlim et al., 2005; Carpiniello et al., 2006; Trompenaars et al., 2005). Similarly, the ACE and GAF scales have not been thoroughly validated. Limitations of this study include the use of a single QoL instrument, which did not allow us to directly compare the WHOQOL-BREF scale with other commonly used instruments like the SF-36, which limits direct comparisons with previous literature. Dunner and colleagues, for example, identified a globally poor QoL in TRD patients by using the SF-36 (Dunner et al., 2006). This may be an important measurement issue, based on evidence that the WHOQOL-BREF and SF-36 may measure different constructs (Huang et al., 2006). Given the severity of illness of this population, additional questionnaires were not feasible without over-burdening study participants. Future studies comparing the WHOQOL-BREF with other QoL instruments (e.g., SF-36 and Q-LES-Q) could be helpful to identify differences, advantages, and disadvantages of various scales for the TRD population. Another limitation of the study was that participants were enrolled at a single site. Our sample was recruited from an academic medical center in the midwest region of the US and was largely Caucasian. This sample, therefore, may not be representative of TRD in other parts of the world. Strengths of this study include the prospective study design, our well-characterized patient sample, and the use of an internationally normed, cross-culturally validated, reliable QoL instrument.

Our findings have implications for future TRD research and clinical care. Clinician ratings of depressive symptoms are traditionally targeted as the primary outcome measure when developing, evaluating, and applying antidepressant interventions. The divergence we found between QoL measures and HDRS ratings raises the possibility that this process of intervention development is not well designed to optimize the QoL of individuals with TRD. One could imagine distinct benefits from diverse interventions. For example, a medication might reduce an individual's depressive symptoms, while mindfulness based cognitive therapy improves her functioning at work, and yoga enhances her physical QoL (Chiesa et al., 2015; Eisendrath et al., 2016; Hauksson, Ingibergsdóttir, Gunnarsdóttir, & Jónsdóttir, 2017; Kenny & Williams, 2007; Sipe & Eisendrath, 2012). Our findings support strategies that target co-primary endpoints, including QoL. This kind of strategy might identify a broader range of effective TRD interventions --e.g., exercise (Greer et al., 2016), diet, yoga (Cabral, Meyer, & Ames, 2011), meditation -- that complement more traditional interventions like medications, cognitive therapies, and brain stimulation therapies. We maintain that the ideal treatment plan does it all -- reducing symptoms, improving social and occupational functioning, and enhancing subjective QoL -- to produce maximal positive impact on individuals with TRD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACE	Adverse Childhood Experience Scale
CGI-S	Clinical Global Impression Severity scale
ECT	electroconvulsive therapy
GAF	Global Assessment of Functioning
HDRS	Hamilton Depression Rating Scale
MGH	Massachusetts General Hospital Massachusetts General Hospital
PHQ-9	Patient Health Questionnaire
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire

QoL	Quality of Life
SF-36	36-Item Short Form Health Survey
TRD	Treatment Resistant Depression
WHOQOL-BREF	World Health Organization Quality of Life scale, brief version
WSAS	Work and Social Adjustment Scale

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Highlights

- Quality of life (QoL) was measured from a well-characterized cohort of individuals with treatment-resistant depression using the WHOQOL-BREF -- a validated, multi-domain, cross-cultural, internationally-normed instrument.
- QoL scores were very low in the physical and psychological domains and moderately low in the social domain.
- QoL scores correlated poorly with patient- and clinician-rated measures of symptoms and social functioning, indicating that those measures cannot serve as proxies for QoL.

Figure 1.

Distributions of WHOQOL-BREF scores in four domains. Each panel shows the distribution of z-scores, calculated based on published international norms, for the sample of subjects with treatment-resistant depression ($N=79$). For example, a z-score of 0 represents QoL at the international mean; a z-score of -2 represents QoL two standard deviations below the international norm. The normative sample was demographically similar to our sample: 53% vs 65% female; mean age 45 vs 49 years; 60% vs 52% married or partnered.

Table 1.

Demographics of the sample

Total Participants	79
Female	51
Male	28
Age, Mean (SD)	49.4 (14.8)
Self-reported race	
White or Caucasian	74
Black or African American	2
Asian	1
Other or mixed	2
Years of education, Mean (SD)	15.74 (2.91)
Employment status	
Full-time	7
Part-time	4
Not employed	13
Student/homemaker	7
Retired	13
Other	35
Household income	
Less than \$25,000	24
\$25,000 – 50,000	20
\$50,001 – 75,000	15
More than \$75,000	17
Marital status	
Married	35
Single	18
Divorced	13
Unmarried partner	6
Widowed	6
Other	1

Values indicate number of participants, unless otherwise indicated

Table 2.

WHOQOL-BREF scores for the sample with treatment-resistant depression (N = 79)

Domain	Mean	SD	Mean transformed*	SD transformed*
Domain 1: Physical health	10.42	2.35	40.11	14.67
Domain 2: Psychological	7.74	2.10	23.40	13.11
Domain 3: Social relationships	10.97	3.32	43.46	20.66
Domain 4: Environment	13.98	2.60	62.37	16.25

* values transformed to a scale ranging 0–100

Table 3.

Univariate analyses of WHOQOL-BREF scores versus clinical instruments

	Physical QoL	Psychological QoL	Social QoL	Environment QoL
<i>Patient-rated</i>				
PHQ-9	−0.258 *	−0.426 **	−0.144	−0.192
WSAS	−0.393 **	−0.281 *	−0.257*	−0.254 *
ACE	−0.190	−0.114	−0.235	−0.299 *
<i>Clinician-rated</i>				
HDRS	−0.086	−0.079	−0.021	−0.259 *
GAF	0.034	0.132	0.019	0.124
CGI-S	0.039	−0.087	−0.07	−0.116 *

*
0.01 < p < 0.05**
p < 0.01

Values represent partial correlations, controlling for age and household income

Table 4.

Multiple regression analysis of clinical instruments as predictors of WHOQOL-BREF domain scores

	Physical	Psychological	Social	Environment
Household income	-	-	1.050 (0.309) **	0.904 (0.235) **
Age	-	0.041 (0.015) *	-	-
PHQ-9	-	-0.185 (0.048) **	-	-
WSAS	-0.175 (0.417) **	-	-0.139 (0.067) *	-
ACE	-	-	-	-0.366 (0.128) **
HDRS	-	-	-	-

Each of the four right-most columns represents a multiple regression model in which the 6 predictors in the left column were included as predictors. Predictors that dropped out of the model during the stepwise procedure are represented by a hyphen. Values represent regression coefficients (SEM).

* 0.01 < p < 0.05.

** p < 0.01.

Table 5.

WHOQOL-BREF domain scores compared to normative values and other neuropsychiatric disorders

Reference	Diagnosis	Country	Physical QoL	Psychological QoL	Social QoL	Environmental QoL
Our results	TRD	USA	10.42 (2.35)	7.74 (2.10)	10.95 (3.31)	13.98 (2.60)
Skevington et al., 2004 *	General population	Total	16.2 (2.9)	15.00 (2.8)	14.3 (3.2)	13.5 (2.6)
Skevington et al., 2004	General population	USA	15.5 (3.2)	13.8 (3.2)	13.2 (3.6)	11.7 (2.7)
Mas-Expósito et al., 2011	Schizophrenia	Spain/ Barcelona	13.25 (2.42)	12.18 (2.86)	10.54 (3.26)	13.24 (2.26)
Garg, Chavan, & Arun, 2011)	Treatment resistant Schizophrenia	India/ Chandigarh	11.2 (2.63)	11.1 (2.79)	11.6 (3.63)	12.2 (2.54)
Liou et al., 2005)	Epilepsy	Taiwan	12.57 (2.84)	11.55 (3.01)	12.42 (2.86)	12.83 (2.64)
Fleck et al., 2000)	Mixed inpatients	South Brazil	13.4 (3.2)	14.5 (2.8)	15.3 (3.6)	13.4 (2.4)
Naumann & Byrne, 2004)	Depression	Australia	12.45 (3.58)	11.63 (3.55)	15.12 (3.05)	14.17 (2.81)
Antunes & Fleck, 2009	Mixed inpatients	Brazil/ Porto Alegre	9.25 (2.62)	9.15 (3.17)	11.06 (3.73)	11.84 (2.35)
Berlim, Pavanello, Caldieraro, & Fleck, 2005)	Major Depression Outpatients	Brazil	10.87 (2.14)	10.16 (2.18)	10.61 (3.07)	10.86 (2.24)
Hirayama et al., 2008)	Advanced Parkinson's Disease	Brazil	10.46 (1.55)	12.22 (2.30)	12.00 (3.84)	13.07 (2.02)

* The normative sample was demographically similar to our sample: 53% vs 65% female; mean age 45 vs 49 years; 60% vs 52% married or partnered