received 2 August 2022 | accepted 6 October 2023 | published 10 October 2023 (in press)

Original Article | ARCHIVOS DE NEUROCIENCIAS

PROSPECTIVE ANALYSIS OF A TRD COHORT OVER A 1-YEAR FOLLOW-UP WITH STANDARD OF CARE IN MEXICO: RESULTS FOR DEPRESSION SEVERITY, TREATMENT RESPONSE, DISABILITY AND QOL FROM THE MULTICENTER, OBSERVATIONAL TRAL STUDY

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Abstract

Introduction: Based on TRAL Mexico subsample, clinical outcomes and Patient-Reported Outcomes (PROs) are reported here. Methods: From 697 patients with MDD recruited from 14 Mexican sites, 140 patients with diagnosis of TRD under standard of care (SOC) were included in the 1-year follow-up. Patients with relevant psychiatric comorbidities or active participation in a clinical trial were excluded. Outcomes were obtained from PROs and clinical assessment scales. Results: Patients were mostly female (82.6%), with a mean age of 47.6 years. Only 44.3% of the patients achieved a clinical response, and remission was around 37% (measured through MADRS). Results from PHQ-9, EQ-5D and SDS show significant symptoms and disability for TRD patients in their everyday life after 1-year of follow-up with SOC. **Discussion**: TRD patients showed a significant burden of the disease, as current SOC fails to deliver clinically meaningful results for the majority of the patients. Response, remission and relapse are far from the desired outcomes. **Conclusion**: Mexico has undertaken relevant and meaningful strategies to improve mental health resources availability, but some unmet needs are yet to be addressed. All involved stakeholders should consider public policies to enhance clinical outcomes and availability of resources.

Keywords: *Mexico, Clinical Outcomes, Treatment-Resistant Depressive Disorder, response, Patient-reported outcomes*.

Background

Major depressive disorder (MDD) is a mental disorder from the depressive spectrum and arguably the most disabling disease worldwide[1]. Beyond the significant global prevalence, this condition poses a challenge to modern societies as it impacts most dimensions of everyday living [2,3]. Although prevalence varies significantly, Latin America (LatAm) seems to be particularly affected by the condition. Previous research showed that Mexico presents lower prevalence values (around 8%) compared to other countries in the region[4]. A major concern with MDD is the development of Treatment Resistant Depression (TRD). TRD can be defined as a failure to respond to two or more antidepressants at therapeutic doses, over an appropriate period of time, within the current depressive episode[5] -although definition remains as a current discussion topic- which also impacts comparability between countries and regions, as well as an increase in the time to diagnosis. It is estimated that TRD develops in 20-30% of MDD patients and response is rarely over 70% with current Standard of Care (SOC) [6–8]. Treatment is the most pressing issue in TRD. Strategies such as combination, potentiation and

augmentation with available therapeutic solutions – ranging from pharmacotherapy to psychotherapy - fail to deliver an adequate clinical outcome in both response, remission and as prevention for relapse [9–11]. The need for more effective treatment is critical as suicidality is a common outcome of TRD, with increased mortality compared to MDD[12]. The proportion of TRD patients with partial or no response to treatment has been highlighted, although values vary significantly depending on the assessment criteria[13,14].

The burden of both MDD and TRD is significant. The impact of the disease goes far beyond the economic and healthcare resource utilization [6,15–17]. Although MDD is a source of obvious burden, this tends to increase significantly in patients developing TRD [6,16,17]. The detrimental effect on daily living has been associated also with humanistic, quality of life (QoL), work-productivity and overall psychosocial dimensions. In this regard, QoL is significantly affected, which is associated with the significant impairment posed by high levels of disability derived by the severe clinical presentation of the disease[18,19].

The TRAL (Treatment Resistant Depression in America Latina) was intended to add to the existing literature in the region in which TRD epidemiological data was lacking. This was a multinational, real-world study aiming to estimate the prevalence of TRD among MDD on follow-up at reference centers in the region. The study provided updates on prevalence of TRD, which was around 30% in MDD patients.

This paper presents the results obtained from the subset of Mexico in the phase 2 of the TRAL study, a 1-year follow-up of TRD patients under SOC.

Objectives

This study has two main objectives:

- To depict a 1-year follow-up of TRD patients in Mexico under Standard-of-care, focused on the characterization of clinical outcomes (depression severity, clinical response, remission and relapse;
- To present the PROs (QoL, disability) for 1-year follow-up of TRD patients in Mexico under Standard-of-care providing key indicators of the burden of the disease.

Methods

Study design and population

TRAL was a multicenter, multinational, observational study conducted in a real-world setting (October 2017 - December 2018) based on reference psychiatric sites from 4 countries (Argentina, Brazil, Colombia, and Mexico). The main purpose of the TRAL's phase 1 was a cross-sectional analysis to portray the epidemiology and disease characterization of TRD in a sample of MDD patients, which constituted the study baseline. Following this, a phase 2 is a 1-year follow-up of TRD patients under SOC for the determination of clinical -depression and suicidality- and safety outcomes, as well as PROs (e.g. work impairment, quality of life, disability). The present analysis depicts the phase 2 data from Mexico, based on a subsample obtained in the country from 13 reference centers (7 public and 6 private sites) providing a broad characterization of the whole country. A full list of sites can be found in previous publications[20].

Patients that were clinically diagnosed with TRD based on both DSM-5 criteria and MINI, and fulfilling the study's TRD definition, were included in the phase 2 (longitudinal) of the study.

Data and assessments

TRD diagnosis was established based on the criteria defined by protocol. Patients had to be followed up adequately and treated with ≥2 antidepressants -at adequate dose and for adequate duration- in the current episode, with an absence of clinical response to treatment based on MADRS [5]. Validated instruments were used for clinical response and Patient Reported Outcomes. Depression severity was assessed with the Montgomery - Åsberg Depression Rating Scale (MADRS) 21, which shows a good discrimination between responders and non-responders to antidepressants, particularly to assess response to SOC over a 1-year time span (more information can be found here)[20].

The Patient Health Questionnaire (PHQ-9), a 10-item questionnaire that characterizes the severity of symptoms on a 4-point scale relative to a pre-defined time frame, usually the last 2 weeks, was also included to assess depression severity [22,23].

Sheehan Disability Scale (SDS) was used to assess functional disability from TRD [24]. A patient that scores 5 or more in any of the SDS scales should be closely monitored since it implies significant functional impairment.

Quality of life was assessed with the EQ-5D-5L questionnaire[25], a 5-dimension questionnaire (Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) which also comprises a global assessment visual analogue 100-point scale. Score were also converted to the EQ-5D-3L score using responses in the EQ-5D-5L index values based on US values set[26].

Sociodemographic (age, sex, marital status and years of education) and clinical features at baseline were collected (age, depression duration and comorbidities) and assessed by a physician, while clinical features were again collected at the end of the study.

Written informed consent was obtained from all participants. The study was approved by local Independent Ethics Committee / Institutional Review Board.

Statistical Analysis

From the initial Mexican sample of 699 MDD included in phase 1, 140 were included in the phase 2 as per the study criteria – diagnosis of TRD and follow-up. Although the sample size is relevant for Mexico, the study was not designed to be representative for each country, but only for the whole region (LatAm). Therefore, inferences should be performed with care. Quantitative variables were summarized as mean, median, standard deviation minimum and maximum, and qualitative variables were summarized as absolute frequency and percentages. Longitudinal comparisons on clinical outcomes were performed with a Generalized estimating equation (GEE) for a 95% Confidence interval. There were no multiple testing corrections performed.

There was no imputation of missing data. Statistical significance was set at 5%. Statistical analysis was performed using SAS® (version 9.4, SAS Institute Inc, Cary).

Results

Patient disposition and sociodemographic characteristics over a 1-year follow-up with SOC for the Mexican subset

From an overall sample of 699 patients with MDD in Mexico, roughly 20% (n=140) were included in phase 2 with a clinical diagnosis of TRD (Table 1). Most of these patients (87.1%) completed the study as planned in the protocol and, for those that did not complete (n=18, 12.9%) the main reason was lost to follow up (n=12, 66.7%).

Most of the sample identified in phase 1 as having TRD were female patients (82.6%), averaging 47.6 years, with more than half (50.7%) married or on consensual union and 33.1% single. Around 40% had at least 13 years of formal education (Table 1).

Clinical outcomes of depression and depression severity in TRD patients over a 1-year follow-up with SOC for the Mexican subset

Montgomery-Asberg Depression Scale (MADRS) in TRD patients over a 1-year follow-up with SOC for the Mexican subset

The average MADRS score at visit 1 was 30.17 (range: 9 to 50) - Table 2. MADRS total score varied significantly over time ($p<0.0001$), with a mean monthly variation of 1.1 points (B=-1.054)).

Almost 27% of the TRD sample had severe depression at visit 1, while at the end of study 10.7% of the patients still presented values consisted with severe depression, with moderate depression representing around 22.1% of the patients. At the end of study visit, 84.3% of the patients still displayed some degree of depressive symptoms.

Less than half (44.3%) of the patients showed a clinically significant response (reduction ≥ 50% in the MADRS total score) at the end of the study visit. As for clinically diagnosed relapse, less than 0.8% of the TRD sample showed values in MADRS consistent with these outcome at the end of study visit after 1-year of SOC, while remission was achieved by less than 37% of the patients (Table 2).

Questionnaire On Patient's Health (PHQ-9) in TRD patients over a 1-year follow-up with SOC for the Mexican subset

The mean total score of PHQ-9 at visit 1 was 17.01 in TRD patients and more than two-thirds (66.7%) of TRD patients had a moderately severe or severe depression). At the end of study the mean score of phase 2 patients (TRD patients) was 10.3 points and 34.5% of patients had their depression classified as moderately severe or severe (Table 3). Moreover, at the end of study, 77.9% of the patients reported having some difficulties conducting their instrumental daily activities.

Quality of life (EQ-5D-5L questionnaire) and Disability (Sheehan Disability Scale - SDS) in TRD patients over a 1-year follow-up with SOC for the Mexican subset

Quality of Life – EQ-5D-5L Questionnaire in TRD patients over a 1-year follow-up with SOC for the Mexican subset

Results from quality of Life can be seen in Table 4 as assessed with EQ-5D. At baseline, 54.9% of the patients reported having no problems walking, 48.6% reported having no problems washing or dressing themselves, 18.8% of the patients revealed no problems doing their usual activities, 27.8% of the patients reported having no pain or discomfort and 3.5% of the TRD patients did not feel anxious or depressed. TRD patients seem

Table 1. Patient disposition and Sociodemographic data at visit 1 (baseline) in the Mexican subset

	TRD (n=144)
Age (years)	
N	144
Mean	47.60
Standard deviation	12.98
Minimum	18.00
Maximum	80.00
Gender, n (%)	
Female	119 (82.6%)
Male	25 (17.4%)
Marital status, n (%)	
Single	47 (33.1%)
Married/Consensual Union	72 (50.7%)
Divorced/Separated	16 (11.3%)
Widower	7 (4.9%)
Total	142
Years of formal education, n (%)	
0	0
1-4 years	0
5-9 years	42 (29.6%)
10-12 years	43 (30.3%)
≥ 13 years	57 (40.1%)
Total	142
Analysis dataset for phase 2 by visit, n (%)	
Visit 1	140 (100.0%)
Visit 2	132 (94.3%)
Visit 3	124 (88.6%)
Visit 4	122 (87.1%)
Visit 5 (end of study)	122 (87.1%)
For patients enrolled in the phase 2	
Patient completed the study as planned into the protocol, n (%)	
No	18 (12.9%)
Yes	122 (87.1%)
Total	140
If no, reason for premature withdrawal, n (%)	
The subject withdraws his consent	2 (11.1%)
The subject is lost to follow up	12 (66.7%)
The subject died	2 (11.1%)
Other reason	2 (11.1%)
Total	18

MDD - Major Depressive Disorder. TRD - Treatment Resistant Depression.

Table 2. Montgomery-Asberg Depression Scale (MADRS) in TRD patients over a 1-year follow-up with SOC for the Mexican subset

	Visit 1 (n=144)	Visit 2 (n=132)	Visit 3 (n=124)	Visit 4 (n=122)	End of study* (n=122)
Total score[a)]					
N	144	132	124	122	122
Mean	30.17	22.16	20.19	19.51	17.64
Standard deviation	8.63	11.16	11.20	11.21	11.87
Minimum	9.00	0.00	0.00	0.00	0.00
Maximum	50.00	45.00	48.00	45.00	48.00
GEE model	50.00	48.00	46.00	49.00	47.00
B (linear regression parameter)	-1.054				
95% CI	[-1.222; -0.885]				
p-value	<0.0001				
Symptom absent (0-6)	0	14 (10.6%)	14 (11.3%)	16 (13.1%)	19 (15.6%)
Mild depression (7-19)	21 (14.6%)	38 (28.8%)	48 (38.7%)	50 (41.0%)	63 (51.6%)
Moderate (20-34)	77 (53.5%)	54 (40.9%)	44 (35.5%)	40 (32.8%)	27 (22.1%)
Symptom absent/ Mild depression/ Moderate (0-34)	98 (68.1%)	106 (80.3%)	106 (85.5%)	106 (86.9%)	109 (89.3%)
Severe depression (35-60)	46 (31.9%)	26 (19.7%)	18 (14.5%)	18 (14.5%)	13 (10.7%)
Change in total score from visit 1 (%)					
N		132	124	122	122
Mean		-25.58	-31.04	-32.53	-39.92
Standard deviation		31.66	34.73	35.92	36.87
Minimum		-100.00	-100.00	-100.00	-100.00
Maximum		75.00	100.00	87.50	100.00
Response (Reduction ≥50% in the total score), n (%)					
yes		24 (18.2%)	32 (25.8%)	38 (31.1%)	54 (44.3%)
Total		132	124	122	122
Remission (MADRS total score ≤12), n (%)					
yes		28 (21.2%)	27 (21.8%)	31 (25.4%)	45 (36.9%)
Total		132	124	122	122
Relapse, n (%)					
yes			6 (4.8%)	5 (4.1%)	1 (0.8%)
			124	122	122

TRD - Treatment Resistant Depression. GEE: Generalized estimating equation. 95%CI: 95% Confidence interval.
a) Range: 0 to 60. Higher values indicate a higher level of depression. *End of study – final visit, after 1-year follow-up

Table 3. Reported analysis of Questionnaire on Patient's Health (PHQ-9) of TRD patients over a 1-year follow-up with SOC for the Mexican subset

	Visit 1 (n=144)	Visit 3 (n=124)	End of study (n=122)	Longitudinal analysis GEE model	
Total score[a]					
N	144	124	122		
Mean	17.01	12.06	10.28		
Median	17.00	11.50	8.00	B (linear regression parameter)	-0.556
Standard deviation	5.49	7.02	7.80	96% CI	[-0.664; -0.447]
Minimum	2.00	0.00	0.00	p-value	<0.0001
Maximum	27.00	27.00	27.00		
Depression severity, n (%)					
None (0-4)	2 (1.4%)	20 (16.1%)	39 (32.0%)		
Mild (5-9)	10 (6.9%)	28 (22.6%)	28 (23.0%)		
Moderate (10-14)	36 (25.0%)	25 (20.2%)	13 (10.7%)		
Moderately severe (15-19)	42 (29.2%)	25 (20.2%)	24 (19.7%)		
Severe (20-27)	54 (37.5%)	26 (21.0%)	18 (14.8%)		
Total	144	124	122		
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?, n (%)					
Not difficult at all	4 (2.8%)	18 (14.5%)	27 (22.1%)		
Somewhat difficult	56 (38.9%)	74 (59.7%)	77 (63.1%)		
Very difficult	65 (45.1%)	31 (25.0%)	16 (13.1%)		
Extremely difficult	19 (13.2%)	1 (0.8%)	2 (1.6%)		
Total	144	124	122		

a) Total score range between 0 and 27 and higher values indicate higher depression severity. MDD - Major Depressive Disorder. TRD - Treatment Resistant Depression. GEE: Generalized estimating equation. 95%CI: 95% Confidence interval.

Table 4. Quality of life - EQ-5D-5L questionnaire over a 1-year follow-up of TRD patients with SOC for the Mexican subset

	Visit 1 (n=144)	End of study (n=122)	Longitudinal analysis GEE model
Mobility, n (%)			
I have no problems walking	79 (54.9%)	81 (66.4%)	
I have slight problems walking	26 (18.1%)	22 (18.0%)	
I have moderate problems walking	35 (24.3%)	18 (14.8%)	
I have severe problems walking	3 (2.1%)	1 (0.8%)	
I am unable to walk	1 (0.7%)	0	
Total	144	122	
Self-care, n (%)			
I have no problems washing or dressing myself	70 (48.6%)	84 (68.9%)	
I have slight problems washing or dressing myself	27 (18.8%)	20 (16.4%)	
I have moderate problems washing or dressing myself	35 (24.3%)	17 (13.9%)	
I have severe problems washing or dressing myself	12 (8.3%)	1 (0.8%)	
I am unable to wash or dress myself	0	0	
Total	144	122	
Usual activities, n (%)			
I have no problems doing my usual activities	27 (18.8%)	60 (49.2%)	
I have slight problems doing my usual activities	38 (26.4%)	31 (25.4%)	
I have moderate problems doing my usual activities	57 (39.6%)	28 (23.0%)	
I have severe problems doing my usual activities	18 (12.5%)	3 (2.5%)	
I am unable to do my usual activities	4 (2.8%)	0	
Total	144	122	
Pain/discomfort, n (%)			
I have no pain or discomfort	40 (27.8%)	55 (45.1%)	
I have slight pain or discomfort	36 (25.0%)	38 (31.1%)	
I have moderate pain or discomfort	44 (30.6%)	24 (19.7%)	
I have severe pain or discomfort	19 (13.2%)	3 (2.5%)	
I have extreme pain or discomfort	5 (3.5%)	2 (1.6%)	
Total	144	122	
Anxiety/depression, n (%)			
I am not anxious or depressed	5 (3.5%)	32 (26.2%)	
I have extreme pain or discomfort	25 (17.4%)	55 (45.1%)	
I am moderately anxious or depressed	59 (41.0%)	25 (20.5%)	
I am severely anxious or depressed	42 (29.2%)	7 (5.7%)	
I am extremely anxious or depressed	13 (9.0%)	3 (2.5%)	
Total	144	122	
Health in the current day[a]			
N	144	122	
Mean	52.90	73.32	
Median	51.50	80.00	B (linear regression parameter) 0.801
Standard deviation	19.56	19.21	95% CI [0.395; 1.207]
Minimum	0.00	20.00	
Maximum	90.00	100.00	
EQ-5D-3L score[b]			
N	144	122	
Mean	0.64	0.79	
Median	0.67	0.82	B (linear regression parameter) 0.012
Standard deviation	0.17	0.16	95% CI [0.009; 0.014]
Minimum	-0.06	0.24	p-value <0.0001
Maximum	1.00	1.00	
Score recoded as categorical variable, n (%)			
Worst health status (score <0.403)	14 (9.7%)	5 (4.1%)	
Higher health status (score ≥0.403)	130 (90.3%)	117 (95.9%)	
Total	144	122	

a) The health in current day was assessed through a visual analogic scale (range 0=worst health to 100=best health).
b) Score was calculated based on response combinations and using US population/scores as a reference.

Table 5. Sheehan Disability Scale (SDS) over a 1-year follow-up of TRD patients with SOC for the Mexican subset

	Visit 1 (n=144)	Visit 3 (n=124)	End of study (n=122)	Longitudinal analysis GEE model	
The symptoms have disrupted your work /school, n (%)					
Not at all	7 (6.4%)	9 (11.5%)	10 (12.7%)		
Mildly	15 (13.6%)	16 (20.5%)	23 (29.1%)		
Moderately	31 (28.2%)	37 (47.4%)	34 (43.0%)		
Markedly	50 (45.5%)	13 (16.7%)	11 (13.9%)		
Extremely	7 (6.4%)	3 (3.8%)	1 (1.3%)		
Total	110	78	79		
N	110	78	79		
Mean	5.91	4.59	4.04		
Median	7.00	5.00	4.00		
Standard deviation	2.75	2.64	2.48		
Minimum	0.00	0.00	0.00		
Maximum	10.00	10.00	10.00		
The symptoms have disrupted your social life/leisure activities, n (%					
Not at all	4 (2.8%)	14 (11.3%)	18 (14.8%)		
Mildly	13 (9.0%)	26 (21.0%)	46 (37.7%)		
Moderately	43 (29.9%)	61 (49.2%)	40 (32.8%)		
Markedly	75 (52.1%)	19 (15.3%)	18 (14.8%)		
Extremely	9 (6.3%)	4 (3.2%)	0		
Total	144	124	122		
N	144	124	122		
Mean	6.45	4.36	3.74		
Median	7.00	4.00	3.00		
Standard deviation	2.29	2.45	2.50		
Minimum	0.00	0.00	0.00		
Maximum	10.00	10.00	9.00		
The symptoms have disrupted your family life/home responsibilities, n (%)					
Not at all	4 (2.8%)	15 (12.1%)	15 (12.3%)		
Mildly	11 (7.6%)	33 (26.6%)	49 (40.2%)		
Moderately	61 (42.4%)	53 (42.7%)	41 (33.6%)		
Markedly	58 (40.3%)	21 (16.9%)	17 (13.9%)		
Extremely	10 (6.9%)	2 (1.6%)	0		
Total	144	124	122		
N	144	124	122		
Mean	6.24	4.23	3.70		
Median	6.00	4.00	3.00		
Standard deviation	2.23	2.37	2.43		
Minimum	0.00	0.00	0.00		
Maximum	10.00	10.00	9.00		
Total score					
N	110	78	79		
Mean	18.68	13.31	12.28		
Median	20.00	15.00	14.00	B (linear regression parameter)	-0.518
Standard deviation	6.56	6.97	7.01	95% CI	[-0.645; -0.390]
Minimum	2.00	0.00	0.00	p-value	<0.0001
Maximum	30.00	30.00	27.00		
On how many days in the past 7 days did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities					
N	144	124	122		
Mean	1.72	1.12	1.04		
Median	1.00	0.00	0.00		
Standard deviation	2.14	1.68	1.65		
Minimum	0.00	0.00	0.00		
Maximum	7.00	7.00	7.00		
On how many days in the past 7 days did you feel so impaired by your symptoms, that even though you went to school or work or had other daily responsibilities, your productivity was reduced					
N	144	124	122		
Mean	2.16	1.52	1.09		
Median	2.00	1.00	0.00		
Standard deviation	2.04	1.69	1.37		
Minimum	0.00	0.00	0.00		
Maximum	7.00	7.00	5.00		

TRD - Treatment Resistant Depression. GEE: Generalized estimating equation. 95%CI: 95% Confidence interval.

to have a positive evolution in most dimension at the end of the study. However, 33.6% of the patients still reported mobility issues, 31.1% had issues with self-care, 50.8% have problems with their usual activities, 54.9% still presented some pain/discomfort and, most importantly, 73.8% still had some anxiety/depression issues.

The mean classification of the overall health for TRD patients was 52.9 points at visit 1 and 73.3 points at the end of study, a statistically significant result ($p<0.0001$).

Sheehan Disability Scale (SDS) in TRD patients over a 1-year follow-up with SOC for the Mexican subset

Table 5 depicts the evolution of values of disability assessed by SDS over 1 year. At visit 1, 6.4% of TRD patients reported that symptoms extremely disrupted their work/school, 6.3% that symptoms extremely disrupted their social life/leisure activities and for 6.9% the symptoms extremely disrupted their family life/home responsibilities. Interestingly, the proportion of patients at the end of study visit varied slightly in most dimensions. Very relevant is the proportion of patients that still reported disruption of work/school activities (87.3%), as well as the 85.2% that still disruption in their social life/leisure activities, and the 87.7 that feel it has disrupted their family/home responsibilities.

The mean total SDS score varied significantly from baseline to the end of study ($p<0.0001$). On average, TRD patients identify that in at least one day in the past 7 days, the condition has impaired in a significant way from performing at school/work or even missing on their responsibilities.

Discussion

This paper follows epidemiological data regarding TRD in Mexico[27]. Within the scope of the TRAL study, Mexico had a significant prevalence of TRD including all patients (20.7%) and only treated patients (23.5%), in line with a high proportion of female patients -over 82%. The present results show that despite the baseline of patients in Mexico -the clinical presentation of the patients seems to be less severe than expected- a significant proportion of the patients do not achieve a clinical response. From a total of around 44% that showed response, almost 37% can be characterized as remitters -contrasting also with the less than 1% of patients with relapse- as assessed with MADRS. Regardless of the outcome, which should be interpreted with caution since sample size was not calculated to allow inferences at a country level, this is still

far from desired outcomes. The analysis of other measures of depression severity, such as PHQ-9, support the evidence that current results achieved with SOC are insufficient. Only about 22% of the patients reported having no difficulties in their everyday life, underscoring the unmet needs in the country and region20. The limited access to mental healthcare services in Mexico may offer some explanation to the results, as the reference centers may be confronted with the need to follow patients that are treatment compliant and willing to participate in a study with 5 longitudinal assessments. Many TRD patients have economic problems, maybe derived from depression among other causes, leading to problems with long follow-ups in Mexico. Also, Mexico has mixed -public and private sector- mental healthcare offer which were evenly included in this study, contrasting somewhat to what is the reality in other countries.

The burden of TRD affects patients in multiple dimensions. The current results show that the assessments based on QoL and disability highlight the need for better outcomes in these dimensions based on the available SOC. The proportion of patients that report on the severe impact of the condition on a daily basis, hindering their independence and adding to the burden of the disease, is high. However, these results are aligned with the vast body of literature available on the subject [6,16–18,28,29]. Considering suicidality, this leads to higher number of hospitalizations, with increased cost and healthcare resources utilization. On the other hand, school/work productivity is limited which impacts also on families and formal and informal caregivers. This impairment is highlighted in the prevalence of depression and anxiety symptoms after 1-year, which underlines the simultaneous nature of depression and anxiety in these patients [30,31].

A significant effort in Mexico has been put in place in the last decade to increase offer in both treatment options and mental health specialists, but there is still some way to go as far as treatment gap [32,33]. This changing trend in the healthcare ecosystem saw improvements in three key areas - prevention, hospitalization and social reintegration- but more effort should be implemented to ensure that objectives are fulfilled [34], namely increased access to primary care[35]. Working on social stigma and ensuring proper patient education is also paramount to the success of the current strategy [36].

The study has some limitations assumed on the study design. Real-world provides a more accurate depiction of the reality in Mexico. However, due to the observational nature of the study some variables were not controlled, and study inclusion criteria may have been impacted by the characteristics of each center in the study. Moreover, only patients already followed at the study centers were included, which may have left some more severe cases out of the study sample. The high proportion of female patients, although expected based on the literature, may impact the overall results, as women tend to have a higher treatment adherence than men[37,38]. Concomitantly, sample size was not designed for inferential analysis and generalization at country level, so data interpretation should be performed with caution. Therefore, this is not a population-based study, as only adults under regular follow-up at medical centers and with a clinical diagnosis of MDD were included in the study.

On the other hand, the depiction of the reality in Mexico is enhanced using real-world evidence, and all procedures were put in place to ensure the maximum level of rigor in the study. Regarding this, it is important to mention the inclusion of a diversity of refence centers with different size, expertise and location -including both private and public sites-, as well as the diversity of patient profile and treatment protocols used. Therefore, the present data constitutes a very important reference data source for future decisions in the healthcare context in Mexico, namely in addressing the current medical and societal unmet needs for TRD patients. This is the first study in Mexico on TRD. On a broader perspective, this study adds to the evidence in support of the development of new treatment protocols for TRD. Also, it is essential to ensure a timely diagnosis and swift medication switch when needed, to avoid the development of more complex and chronic clinical presentations. More psychiatrists are needed in Mexico, as well as a more balanced distribution of healthcare resources -namely the availability of therapeutics in all regions-, suggesting that more investment in mental health is needed.

Further research

Future research on the subject should provide a comparative approach to different therapeutics available in Mexico, not only focused on clinical outcomes but also on treatment adherence, patient reported outcomes and other unmet needs in the context of mental healthcare for TRD patients in Mexico. Also of interest is the possibility of performing sub-group analysis that allow the identification of factors associated with good prognosis, as well as to understand the subtleties of the variation in values for the PRO based on patients achieving response/non-response to treatment.

Conclusions

The burden of TRD in LatAm is significant. Available clinical protocols based on standard of care do not provide the necessary clinical outcomes for those in need. Due to the life-threatening nature of TRD, associated with high levels of suicidality, a urgent call to action is necessary which includes all relevant stakeholders and decision makers in Mexico to ensure proper measures are enforced. The action plan should also consider that the burden of disease strains the already limited healthcare resources on mental health existent in the country, as well as caregivers and patients alike. Effort should also be placed on achieving a scientific consensus on the definition of TRD that leads to an easier operationalization of screening, diagnosis, and treatment. Results from the TRAL study have the potential to become a relevant decision-making supporting tool to ensure adequate decisions and aid for those in need in Mexico.

Acknowledgments

The authors would like to thank all TRAL investigators and site coordinators, as well as the patients and their families. Clinical Trial & Consulting Services (CTI) provided statistical analysis support to the TRAL funded by Janssen LatAm.

Diogo Morais from Clinical Trial & Consulting Services (CTI) provided medical writing assistance and editorial support with this manuscript, funded by Janssen LatAm. Janssen LatAm participated in the interpretation of data, review, and approval of the content. All the authors had access to all relevant data and participated in writing, review, and approval of this manuscript.

Conflict of Interest

1.JZ: declares no conflict of interests
2. JLVH: declares no conflict of interests
3. FFBR: declares no conflict of interests
4.LDAS: researcher for "Avalon-Vinculación Médica en Salud Mental", in which he is the principal investigator and sub-investigator of several protocols of original epidemiological research of the institution. Has received professional fees for the time spent on subject interviews in the present study by Janssen Research & Development, as approved by the Independent Research Ethics Committee. Dr. Alviso has work as speaker, collaborated in advisory boards, or received scientific fees from: Janssen, Pfizer, Sanofi Aventis, Schwabe-Pharma, Novartis, Lundbeck, Roche, Lilly, Asofarma, Psicofarma, Ferrer, Servier, and Shire
5.GK: Is currently an employee at Janssen Pharmaceutical
6.SP: At the time of this research, SP was an employee at Janssen Pharmaceutical

Financial support statement

TRAL (Treatment-Resistant Depression in America Latina) study was funded by Janssen Latin America. CTI provided medical writing and editorial support funded by Janssen Latin America.

Author Contribution

All authors contributed significantly to the design of the study and interpretation of the data. All the authors reviewed the final manuscript and approved the content.

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