

PERCEIVED COGNITIVE DYSFUNCTION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER IN PAKISTAN: A CROSS-SECTIONAL STUDY

FAREED ASLAM MINHAS¹, RUSHAM ZAHRA RANA², MOWADAT HUSSAIN RANA³, SYED USMAN HAMDANI⁴, IMTIAZ AHMAD DOGAR⁵, MUHAMMAD IQBAL AFRIDI⁶, NAEEM ULLAH LEGHARI⁷, ASAD TAMIZUDDIN NIZAMI⁸, GHULAM RASOOL⁹, KHALID A. MUFTI¹⁰

¹Co-Chairman, Board of Advanced Studies & Research, Rawalpindi Medical University, Director, WHO Collaborating Center and Director, Center for Global Mental Health Pakistan

²Clinical and Health Psychologist and Research Fellow at IMPACT, Institute of Psychiatry, & WHO collaborating Centre, Benazir Bhutto Hospital Rawalpindi, Pakistan

³Professor of Psychiatry, Chief Editor, Journal of Pakistan Psychiatric Society and Chairman, The Healing Triad

⁴University of Liverpool, UK and Human Development Research Foundation, Pakistan.

⁵Professor of Psychiatry Allied Hospital, Faisalabad

⁶Professor of Psychiatry Jinnah Post Graduate Medical Centre, Karachi

⁷Associate Professor and HOD, Department of Psychiatry, Nishtar Medical University, Multan

⁸Head Institute of Psychiatry, WHO Collaborating Centre for Mental Health Research & Training, Rawalpindi Medical University, Rawalpindi

⁹Head of Psychiatry BMC, and Executive Director Baluchistan Institute of Psychiatry and Behavioral Sciences, Quetta

¹⁰Chief Executive Ibadat Hospital, Peshawar

CORRESPONDENCE: PROFESSOR FAREED ASLAM MINHAS, E-mail: minhas.fa@gmail.com

Submitted: May 07, 2019

Accepted: May 31, 2019

ABSTRACT

OBJECTIVE

To explore the existence and impact of perceived cognitive dysfunction in patients suffering with major depressive disorder, to investigate the association between severity of depression and perceived cognitive dysfunction and finally to see whether there is an association between severity of depression and functional disability.

STUDY DESIGN

Correlational study

PLACE AND DURATION OF STUDY

This multi-centred study was conducted from April to October, 2018 in 19 Psychiatry outpatient clinics from all over Pakistan.

SUBJECTS AND METHODS

2599 patients with a positive diagnosis of Major Depressive Disorder were explored using scales measuring depression, perceived cognitive dysfunction and functional disability.

RESULTS

Results showed that a large majority of patients suffered from cognitive dysfunction and that there exists, a positive relationship between depression severity, perceived cognitive dysfunction and functional disability.

CONCLUSION

The study allowed valuable insight into how cognitive dysfunction relates to depression severity and everyday functioning of patients.

KEY WORDS

Perceived cognitive dysfunction, Functional Disability, Major Depressive Disorder

INTRODUCTION

Depressive disorders including major depression are one of the leading causes of disability, globally (Whiteford et al., 2015)¹. Major depressive disorder (MDD) is characterised by physical, emotional and cognitive symptoms that affect people's daily functioning and quality of life (Rock et al., 2014; Ferrari et al., 2013)^{2,3}.

Apart from the effects that MDD has on daily functioning and social relationships, MDD also impairs work productivity and work performance causing absenteeism and disability, adding to the national economic burden (Greenberg et al., 2015)⁴. Studies have shown that MDD has a detrimental effect on cognitive function (Lam et al., 2014)⁵ and that it may act as one of the key determinants of functional impairment in MDD (McIntyre et al., 2013)⁶. 94% of patients suffering from a depressive episode, experience cognitive detriments (Trivedi & Greer, 2014)⁷. Cognitive dysfunction or 'brain fog' refers to a loss in the executive functions of the brain, mainly in attention, learning, memory, reasoning capabilities, problem solving and motor functioning (Millan, Agid et al. 2012)⁸. Most patients suffering through a major depressive episode present with cognitive complaints. These complaints remain, even when patients are in remission and hinder social and professional reintegration (De Vries & Schene, 2015)⁹. Cognitive dysfunction causes and maintains psychosocial impairment and may result in unhealthy lifestyle choices, lower productivity, a higher risk of suicide and poorer treatment outcomes. Qualitative accounts of patients with depression suggest that patients prioritise treatment of cognitive aspects of quality of life over complete symptomatic remission (Papakostas, 2014)¹⁰.

In an emerging economy like Pakistan, there is a growing need for cognitively skilled labour. Patients with MDD and cognitive dysfunction are at a disadvantage and may not receive the same employment opportunities. Given the growing number of people now being diagnosed with depression, a large proportion of the population may essentially, become obsolete. Cognitive impairments underlying

depression remain misunderstood and sub optimally treated. Current treatment plans, are therefore not fully efficacious.

Studies investigating depression and cognitive dysfunction, particularly in Pakistan are rare and long since been updated. To the authors' knowledge, only one other study has been conducted so far, investigating depression and its correlates in Pakistan (Afridi, Hina, Qureshi & Hussain, 2011)¹¹. No study, however, has focused on exploring cognitive dysfunctions in MDD. The present study, thus, is the first of its kind and aims to add to the insufficient empirical evidence regarding the existence and impact of cognitive dysfunction in patients suffering with Major depression as well as to explore the associations between depression severity, perceived cognitive dysfunction and functional disability.

Keeping the gap in research in mind, this study has the following objectives:

- 1) To study the existence and impact of perceived cognitive dysfunction in patients suffering from MDD.
- 2) To explore the association between severity of depression and perceived cognitive dysfunction.
- 3) To explore the association between severity of depression and functional disability

SUBJECTS AND METHODS

Participants

The study was a multi-centred, cross-sectional study, conducted in 19 Psychiatry outpatient clinics with more than 35 investigators from all over Pakistan including Rawalpindi, Faisalabad, Peshawar, Quetta, Swat, Wah, Multan, Lahore, Karachi and Hyderabad from April to October, 2018. 2599 participants aged 18-65, both male and female, attending outpatient clinics and diagnosed with an active episode of major depression using ICD-10 criteria, were selected using convenient sampling.

Patients were excluded if they had a present diagnosis or past medical history of schizophrenia, bipolar disorder, dementia or other neurodegenerative disease, alcohol or substance use/dependence, or any other psychiatric disorder that could affect cognitive functioning such as intellectual disability, acutely suicidal, pregnant or 6 months post-partum or using any psychotropic medication. Patients with any physical condition that could cause cognitive dysfunction such as head trauma and chronic illnesses (Diabetes, hypertension, anaemia, epilepsy, cerebrovascular accident etc.) were also excluded.

Instruments

Clinical Global Impression-Severity scale (CGI-S): Severity of depression was measured by both, clinician and patient reported outcomes. The clinician completed the Clinical Global Impression-Severity of illness scale (CGI-S)¹² (Busner and Targum 2007). CGI-S is a standardised assessment tool for rating severity of an illness on a 7 points scale, where 1 indicates normal health and 7 indicates extreme illness.

Patient health questionnaire-9 (PHQ-9): Patient Health Questionnaire (PHQ-9- Husain et al., 2006)¹³. PHQ-9 is a 9 items scale, with each item scored from 0 (not at all) to 3 (nearly every day). Total

score ranges from 0 to 27. A high score indicates higher depressive symptoms. Scores between 10-14 indicate mild depression, 15-19: moderate depression and 20-27 indicate severe depression.

Perceived Deficits Questionnaire (PDQ): Cognitive dysfunction was assessed using perceived deficits questionnaire (PDQ- Lam et al., 2018)¹⁴. PDQ has 20 items, distributed in four domains: (a) Attention/concentration, (b) retrospective memory, (c) prospective memory and (d) planning/organization. Each item is rated on 0-4 scale. Total score ranges from 0-20 for each sub-scale. Higher scores indicate poorer cognitive functioning.

WHO Disability Assessment Schedule 2.0 (WHODAS): Functional impairment was measured by the WHODAS (World Health Organization 2010)¹⁵. It is a 12-item scale assessing health-related difficulties across domains of functioning. Difficulties were scored on a 5-point scale over the past 30 days. The scores assigned to each of the items – “none” (0), “mild” (1) “moderate” (2), “severe” (3) and “extreme” (4) – are summed. In addition to 12 items, 3 items inquired about the extent to which the various difficulties that patients encountered, have affected their lives.

Procedure

Ethical approval for the study was obtained from the Institutional Research and Ethics Forum (IREF), Rawalpindi Medical University and Allied Hospitals, Rawalpindi, Pakistan. Signed informed consent was obtained from all participants for participation in the study.

Prior to the commencement of the study, all research assistants underwent a one-day structured training session in the administration of outcome measures so as to reduce assessor bias. Patients who presented at the out-patient clinics of the study sites were examined by the attending clinician (the psychiatrist or trainee psychiatrist on-call). After clinical evaluation, patients who were perceived by the clinicians to have an active episode of MDD and fulfilled the eligibility criteria were asked to participate in the study. Subsequent to receiving informed consent, two scales to measure severity of depression were administered. To ensure a true diagnosis of depression the participants first rated themselves using a PHQ-9 test and then were rated by research assistants on the CGI-Severity scale. Patients who scored higher than a 5 on the CGI scale and higher than 10 on the PHQ-9 were then eligible for the second battery of tests (WHODAS and PDQ). Research assistants then recorded the patients' demographic information and administered the other psychometric assessment tests to measure functional disability, and perceived cognitive dysfunction. In the cases where participants were illiterate or unable to complete the tests themselves, the research assistants read out the statements to the participants and wrote down their responses. All data was collated and analysed using SPSS version 21. The demographic characteristics were summarized as the mean, standard deviation and range for continuous, approximately symmetric variables; medians, interquartile range and range for continuous, skewed variables; frequencies and percentages for categorical variables. For continuous outcomes, histograms were plotted to assess normality, and whether any transformation is required. Descriptive analysis was conducted to identify the percentage of patients with depression severity. Pearson's correlation analysis was conducted to explore the relationship among severity of depression, perceived cognitive

dysfunction and functional disability. One-way ANOVA was conducted to explore the association among the severity of perceived cognitive dysfunction as assessed by total PDQ-D and functioning as assessed by WHODAS with demographic variables including: gender, age, living area, education, marital status. CROSSTABS was done to find out interrelationships and interactions between categorical variables including categories of depression with demographic variables including living area, education, marital status and work status had significant value of Pearson Chi-Square, which means variables are independent of each other. Missing data was treated as.

RESULTS

Patients had a mean age of 35.48 ± 11.07 (121 patients were over the age of 60 and 23 were under the age of 20), 39.3% patients were between 31-42 years. 59 % patients were married and 62 % patients were living in urban settings. 64.2% patients were living independently in community. 57.6 % patients were females and 36.3 % were house wives (see table 1).

Table 1
Descriptive data of participants

Treatment status	N (%)
No	1894 (73)
Yes	705 (27)
Receiving psychotherapy	288 (11.1)
Receiving pharmacotherapy	630 (24.2)
TCAs	50 (1.9)
SSRIs	583 (22.4)
SNRI	54 (2.1)
Education	N (%)
No education	632 (24.3)
Primary	283 (10.9)
Middle	234 (9)
Matric	485 (18.7)
Intermediate	400 (15.4)
University	514 (19.8)
Other	43 (1.7)
Missing	8 (0.3)
History of previous depressive episode (N=691) (Mean= 2.4, S.D=1.7)	N (%)
One episode	277 (40)
Two episodes	231 (33.42)
Three episodes	183 (26.4)
Duration of current episode (N=2593)	N (%)
Less than one week	36 (1.4)
One-two weeks	220 (8.5)
Three-four weeks	473 (18.2)
Five-eight weeks	568 (21.9)
More than eight weeks	1296 (49.9)

Many patients were on multi-modal treatment including psychotherapy and pharmacotherapy with more than one class of anti-depressants, hence, the treatment numbers don't add up to the total sum.

Table 2. shows the existence and distribution of cognitive dysfunction in patients diagnosed with MDD. The largest proportion of cases was from Punjab and the lowest from Azad Jammu and Kashmir.

Table 2
Province wise distribution of cognitive dysfunction

Province	Cases (%)
Punjab (10)	1442 (55.6%)
Baluchistan (1)	315 (14.2%)
Sind (4)	322 (13.5%)
Khyber Pakhtunkhwa (3)	398 (12.4%)
Azad Jammu and Kashmir (1)	120 (12.1%)
Total (19)	2599(100%)

Table 3 showed the correlational analysis conducted. Results showed a positive relationship between depression severity, perceived cognitive dysfunction and functional disability, as shown by Pearson's correlations coefficients.

A positive relationship is seen between depression severity with perceived cognitive dysfunction (r=0.619) and functional disability (r=0.663) while perceived cognitive dysfunction also has a positive correlation with functional disability (r=0.700) as shown by Pearson's correlation coefficients.

Table 3
Correlations between depression severity, perceived cognitive dysfunction and functional disability (n=2599)

	PHQ-9	PDQ	WHODAS-12
PHQ-9	-	.619**	.663**
PDQ	-	-	.700**
WHODAS-12	-	-	-

** Correlation is significant at the 0.01 level (2-tailed)

Table 4 shows that the majority of the participants reported moderate (36.4%) to severe (33.4%) depression as assessed by PHQ (total PHQ-9 score [mean ± SD]: 17.44 ± 4.64).

Table 4
Descriptive statistics of PHQ-9 Categories (N=2599)

PHQ-9 Categories	f(%)
No depression (0-4)	-
Mild depression (5-9)	19 (7%)
Moderate depression (10-14)	769 (29.4%)
Moderately severe depression (15-19)	952 (36.4%)
Severe depression (20-27)	873 (33.4%)

Patients reported a mean total PDQ-D score of 40.41 ± 15.064; 70.7% (1850/2599) of the study population had a PDQ-D score ≥ 32. PDQ-D score range (mean ± SD) by quartile as seen in Table 5.

Table 5
Patient's PDQ scores

1st quartile (n=62)	0-9 (5.26 ± 2.717)
2nd quartile (n=163)	10-19 (15.28 ± 2.849)
3rd quartile (n=532)	20-31 (26.75 ± 3.239)
4th quartile (n=1850)	32-80 (47.83 ± 10.393)

For sub-group analysis, we used one-way analysis of variance (ANOVA) (for more than 2 categories of group) and independent-samples t-test (with two categories of group). It was used to determine whether there was any statistically significant difference between the means of subgroup. Subgroup analyses showed significantly higher perceived cognitive dysfunctional scores for patients who were younger (aged 18-30, aged 31-42, PDQ-D: 40.26 ± 15.379 vs 39.87 ± 15.115 respectively) [F (3, 2294)=3.185, p=0.023], living in small towns (PDQ, 43.51 ± 14.668) [F (2, 2592)=13.553, p=0.000], divorced (PDQ, 44.45 ± 15.319) [F (4, 2593)=3.619, p=0.006], unemployed due to health condition (PDQ, 42.82 ± 15.634) and were retired (PDQ, 42.82 ± 13.179) [F (9, 2588)=3.221, p=0.001]

Subgroup analyses showed significantly higher depressive symptoms scores for patients who: were equal to or more than 55 years old (PHQ, 18.44 ± 4.397) [F (3, 2294)=3.037, p=0.028], living in small towns (PHQ, 18.20 ± 4.936) [F (2, 2591)=9.803, p=0.000], had education of 8 or more years (PHQ, 18.22 ± 4.754) [F (7, 2589)=3.960, p=0.000], were separated (PHQ, 18.05 ± 5.156) [F (4, 2592)=2.509, p=0.040] or unemployed due to health conditions (PHQ, 18.16 ± 5.159) [F (9, 2587)=4.179, p=0.000].

Subgroup analyses showed significantly higher functional disability scores for patients who: were equal to or more than 55 years (WHODAS, 39.65 ± 9.556) [F (3, 2294)=7.940, p=0.000], using tobacco (WHODAS, 37.17 ± 9.074) [t (2592)=2.100, p=0.036] living in small towns (WHODAS, 38.10 ± 10.005, [F (2, 2592)=12.397, p=0.000], had education of 8 or more years (WHODAS, 38.06 ± 9.271), [F (7, 2590)=7.990, p=0.000], divorced (WHODAS, 39.84 ± 10.715) [F (4, 2593)=3.527, p=0.007] or retired (WHODAS, 38.08 ± 8.483) [F (9, 2588)=8.675, p=0.000].

DISCUSSION

This study was conducted to explore cognitive dysfunction in patients suffering with an episode of Major depression as well as to explore the associations between depression severity, perceived cognitive dysfunction and functional disability. This study conducted on a total of 2599 from across Pakistan has shown that a high percentage amongst them experience cognitive dysfunction.

The study also reveals a positive relationship between depression severity, perceived cognitive dysfunction and functional disability. Conradi (2011) had shown that 94% patients in his study experienced cognitive dysfunction¹⁶. A relatively higher proportion in his study endorses that cognitive dysfunction in patients of depression is almost a constant feature. A lesser percentage in our sample could be on account of the sensitivity of the two different psychometric tools used, as well as the difference in severity of depression in the two places.

Our study highlights that more than two third patients who receive a diagnosis of MDD harbor cognitive dysfunction. By examining participants with both PHQ-9 and CGI(S) we were able to improve identification of patients at risk. Since a routine screening for the diagnosis of depression does not include testing for cognitive dysfunctions, this important correlate is missed regularly. This has serious clinical implications as no attempts are made in the management plan to alleviate this disabling correlate of depression. This is even more crucial when effective pharmacological and nonpharmacological interventions are available for the management of cognitive dysfunctions. The existing ignorance amongst clinicians is therefore bound to increase the existing treatment gap in managing depression.

While patients suffering from all grades of depression severity frequently report concentration and memory lapses, it is for the first time in Pakistan that a statistical correlation between severity of depression and cognitive dysfunction has been studied, and established statistically in a local study. Afridi et al., (2011) had studied a relationship using less robust psychometric tools but similar decline in cognitive dysfunctions was reported¹¹. Their study was conducted in a hospital-based sample from a tertiary care facility from Karachi, (a megapolis in the South of Pakistan) alone. Our study, however, has gone further to also study functional disability, (ii) perceived cognitive dysfunction with functional disability. Previous researches by Braun et al., (2010) and McIntyre et al., (2013) have also shown the presence of such a correlation⁶. This observation gains significance as when the three correlates are experienced simultaneously they are bound to make each other worse and have a qualitatively negative impact on the patient's mental state. Left unaddressed, this may have long term implications on prognosis.

This study suggests the existence and significant impact of cognitive dysfunction which was consistent with findings from studies conducted worldwide. The results revealed a positive relationship between perceived cognitive dysfunction, depression severity and functional disability whereby, as cognitive dysfunction and depression severity worsened, so did functional disability. Factors associated with disability among patients with depression were mainly old age, marital status, education and urban environment, which is in line with previous research conducted investigating these factors (Ladin, 2008; Miech & Shanahan, 2000; Pearlin, 1975; Boughton, 2011)¹⁸⁻²¹. These findings suggest the need for future treatment plans and interventions to focus on cognitive dysfunction as much as on depressive symptoms. The need to do so is even higher in patients with severer depression, functional disability, and older age.

In comparison to other psychiatric disorders such as Schizophrenia, relatively little importance is given to the risks that cognitive dysfunction poses to MDD. The study was the first of its kind to assess and describe cognitive dysfunction in patients suffering from MDD in Pakistan and added to the limited evidence base in this area. The study allowed valuable insight into how cognitive dysfunction relates to depression severity and everyday functioning of patients.

LIMITATIONS OF THE STUDY

Although a large number of participants were included, from multiple centres, caution must be taken before making

interpretations and inferences of causality due to the lack of controls and methodological constraints in the study. Due to the study being cross sectional, the timing at which the particular study was conducted does not guarantee to be a true representation, as the study was run only in the summer months. This is of serious consideration as major depression is known to have seasonal variations. The generalisability of these results, may also be limited due to heterogeneity of the study population and differences in the sample size between centres. The study used a measure of perceived cognitive dysfunction but measures of specific cognitive decline and regression analysis were not conducted. This limits the predictive validity of our study.

CONCLUSION AND CLINICAL IMPLICATIONS

This study is a step towards early identification, management and possible prevention of cognitive dysfunction in patients of MDD. Keeping in mind the increasing burden of depression in the country, it also provides impetus to identify both objective and subjective, valid and reliable measures of cognitive functions in order to personalise treatment plans. The results of the study highlight the need for evaluation of cognitive functioning as an integral part of management of MDD patients in Pakistan. Future studies should focus on interventions to reduce cognitive deficits in hopes to improve health outcomes and illness trajectory in patients with MDD. Future studies should focus on interventions to reduce cognitive deficits in hopes to improve health outcomes and illness trajectory in patients with MDD. Future studies should also use more potent measures of cognitive dysfunction and undertake regression analyses of the possible risk factors that contribute towards cognitive decline in patients of MDD.

ACKNOWLEDGEMENTS

The authors of this study would like to thank Dr. Adil Afridi (Assistant Psychiatry, Leady Reading Hospital, Peshawar), Dr. Ali Ahsan Mufti (Assistant Professor, Jinnah Medical College, Peshawar), Dr. Alibux Rajper Post Graduate Trainee, Jinnah Post Graduate Medical Centre, Karachi), Dr. Altaf Qadir Khan (Professor of Psychiatry and Head of Department, Ammeeruddin Medial College, Lahore), Dr. Aniq Shafi (Post Graduate Trainee, Allied Hospital, Faisalabad), Dr. Asad Ullah Khan (Consultant Psychiatrist), Dr. Ayesha Minhas Assistant Professor, Institute of Psychiatry, Benazir Bhutto Hospital), Dr. Bushra Razzaque (Senior Registrar, Institute of Psychiatry, Benazir Bhutto Hospital, Dr. Fatima Aamir Khan (Consultant Psychiatrist, POF Hospital, Assistant Professor Department of Psychiatry & Behavioural Sciences Wah Medical College), Dr. Hazarat Ali (Senior Registrar, Baluchistan Institute of Psychiatry and Behavioral Sciences, Quetta), Dr. Khalid Mahmood (Consultant Psychiatrist, Arrahma Hospital for Mental Health, Multan), Dr. Mahmood Ali Khan Jafri (Senior Registrar, Institute of Psychiatry, Benazir Bhutto Hospital), Dr. Mohammad Azeem Rao (Senior Registrar, Institute of Psychiatry, Benazir Bhutto Hospital), Dr. Mohammad Fahim Qasim (Assistant Professor, Head Department of Psychiatry and Behavioral Sciences, Wah Medical College, Wah Cantt), Dr. Muhammad Asif Kamal (Assistant Professor, Department of Psychiatry, Gajju Khan Medical College, Swabi), Dr. Muhammad Kashif (Assistant Professor, Institute of Psychiatry, Benazir Bhutto Hospital), Dr. Neuroze Ali (Senior Registrar Services Hospital, Lahore), Dr. Owais Kareem (Senior Registrar, Department of Psychiatry, Nishtar Medical University Multan), Dr. Qasim Mujahid

(Post Graduate Trainee, Institute of Psychiatry, Benazir Bhutto Hospital), Dr. Rehmat Ali Wogan (Assistant Professor Psychiatry, Shaheed Mohtrama Benazir Bhutto Medical University, Larkana), Dr. S.Qalb i Hyder Naqvi (Psychiatrist, Sir CJ Institute of Psychiatry, Hyderabad), Dr. Sabahat Hameed (Consultant Psychiatrist, Quaid e Azam international Hospital), Dr. Sadia Yasir (Senior Registrar, Institute of Psychiatry, Benazir Bhutto Hospital Rawalpindi), Dr. Shakeel Asif (Assistant Professor, Department of Psychiatry, Gajju Khan Medical College, Swabi), Dr. Sumaira Qambar (Associate Professor, Services Hospital, Lahore), Dr. Zaidan Idrees Choudhary (Assistant Professor, Aziz Fatimah Medial & Dental College, Faisalabad), Dr. Zainab Nawaz (Senior Registrar, Gajju Khan Medical College, Swabi), Dr. Zainullah Khan (Kakar Senior Registrar Baluchistan Institute of Psychiatry and Behavioral Sciences, Quetta), Ms. Abida Nazir (Clinical Psychologist, Sarhad Hospital for Psychiatric Diseases, Peshawar), Ms. Sana Ashraf (Clinical Psychologist, Tree House Psychiatric Clinic), Prof. Moin Ansari (Professor and Chairman Department of Psychiatry LUMHS and Sir Cowasjee Jehangir Institute of Psychiatry, Hussainabad, Hyderabad) without whose contribution to the data collection and analysis, this study would not have been possible.

CONFLICT OF INTEREST

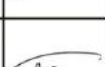
This study was supported by an investigator-initiated grant to Center for Global Mental Health by Lundbeck.

REFERENCES

1. Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. *PLoS one*. 2015 Feb 6;10(2):e0116820.
2. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological medicine*. 2014 Jul;44(10):2029-40.
3. Ferrari AJ, Somerville AJ, Baxter AJ, Norman R, Patten SB, Vos T, Whiteford HA. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychological medicine*. 2013 Mar;43(3):471-81.
4. Greenberg P E, Fournier AA, Sisitsky T, Pike C T, Kessler R C. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *The Journal of clinical psychiatry*. 2015;76(2):155-162.
5. Lam RW, Kennedy S H, McIntyre R S, Khullar A. Cognitive dysfunction in major depressive disorder: effects on psychosocial functioning and implications for treatment. *The Canadian Journal of Psychiatry*. 2014; 59(12): 649-654.
6. McIntyre RS, Cha DS, Soczynska JK, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety*. 2013;30:515-527. *Miech*, R.
7. Trivedi M H, Greer T L. Cognitive dysfunction in unipolar depression: implications for treatment. *Journal of affective disorders*. 2014;152:19-27.
8. Millan MJ, Agid Y, Brüne M, Bullmore ET, Carter CS, Clayton NS, Connor R, Davis S, Deakin B, DeRubeis RJ, Dubois B. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nature reviews Drug discovery*.

2012 Feb;11(2):141.

9. de Vries G, Schene A H. Reintegrating People Suffering from Depression into the Workplace. In International Handbook of Occupational Therapy Interventions (pp. 697-708). Springer, Cham. 2015.
10. Papakostas GI. Cognitive symptoms in patients with major depressive disorder and their implications for clinical practice. J Clin Psychiatry. 2014;75(1):8-14.
11. Afridi MI, Hina M, Qureshi IS, Hussain M. Cognitive disturbance comparison among drug-naive depressed cases and healthy controls. Journal of the College of Physicians and Surgeons-Pakistan. 2011;21:351-355.
12. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7):28.
13. Husain N, R. Gater, B. Tomenson and F. Creed (2006). "Comparison of the personal health questionnaire and the self-reporting questionnaire in rural Pakistan." Journal-Pakistan Medical Association 56(8):366.
14. Lam R W, Lamy F X, Danchenko N, Yarlak A, White M K, Rive B, Saragoussi D. Psychometric validation of the Perceived Deficits Questionnaire-Depression (PDQ-D) instrument in Us and UK respondents with major depressive disorder. Neuropsychiatric disease and treatment. 2018; 14:2861.
15. WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) [Internet]. World Health Organization. 2010. Available from: <https://www.who.int/classifications/icf/whodasii/en/>
16. Conradi HJ, Ormel J, de Jonge P. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. Psychol Med. 2010;8:1-10.
17. Braun M, Mura K, PETER - WIGHT ME, Hornung R, Scholz U. Toward a better understanding of psychological well - being in dementia caregivers: the link between marital communication and depression. Family process. 2010 Jun;49(2):185-203.
18. Ladin K. Risk of late-life depression across 10 European Union countries: deconstructing the education effect. Journal of aging and health. 2008; 20(6):653-670.
19. Miech RA, Shanahan MJ. Socioeconomic status and depression over the life course. Journal of Health and Social Behavior. 2000 Jun 1:162-76.
20. Pearlman LI. Sex roles and depression. In Life-span developmental psychology (pp. 191-207). Academic Press. 1975.
21. Boughton S, Street H. Integrated review of the social and psychological gender differences in depression. Australian Psychologist. 2011;42(3):187-197.

Sr.	Author Name	Affiliation of Author	Contribution	Signature
1	Fareed Aslam Minhas	Professor of Psychiatry Member Syndicate Co-Chairman, Board of Advanced Studies & Research Rawalpindi Medical University Director, WHO Collaborating Center Director, Center for Global Mental Health Pakistan Rawalpindi	Author	
2	Rusham Zahra Rana	Rusham Zahra Rana Clinical Psychologist	Co- Author	
3	Mowadat Hussain Rana	Professor of Psychiatry, Chief Editor, Journal of Pakistan Psychiatric Society Chairman, The Healing Triad	Co- Author	
4	Usman Hamdani	Consultant Psychiatrist, HDRF Centre for Global Mental Health, Rawalpindi	Co- Author	
5	Imtiaz Dogar	Professor of Psychiatry, Allied Hospital Faisalabad	Co- Author	
6	Muhammad Iqbal Afridi	Professor of Psychiatry, Jinnah Post Graduate Medical Centre, Karachi	Co- Author	
7	Naeem Ullah Leghari	Associate Professor and HOD, Dept of Psychiatry, Nishtar Medical University Multan	Co- Author	
8	Asad Tamizuddin Nizami	Professor of Psychiatry, Head Institute of Psychiatry, Benazir Bhutto Hospital, Rawalpindi	Co- Author	
9	Ghulam Rasool	Professor of Psychiatry, Head of Psychiatry BMC, and Executive Director, Baluchistan Institute of Psychiatry and Behavioral Sciences, Quetta	Co- Author	
10	Khalid A. Mutti	Professor of Psychiatry, Chief Executive Ibadat Hospital (Pvt Ltd), Chairman Horizon NGO (Mental Health & Drug Dependencies welfare) Zone 15 Representative WPA, Chair South East Asian Division of The Royal College of psychiatrists UK, Peshawar	Co- Author	