



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

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## ABSTRACT

**OBJECTIVE**

To explore the existence and impact of perceived cognitive dysfunction in patientssuffering 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 ANO 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 dysfunctionandfunctionaldisability.

## CONCLUSION

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

## KEYWORDS

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)'. Major depressivedisorder(MOD) ischaracterised by physical, emotional and cognitive symptoms that effect people'sdaily functioning andquality of life (RocketaI., 2014;Ferrariet al.,2013)'-'.

Apart from the effects that MOD 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)'. Studies have shown that MOD hasa detrimental effect on cognitive function (Lam et al., 2014)' and that it may act as one of the key determinants of functional impairment in MOD (McIntyre et al., 2013)'. 94% of patients suffering from a depressive episode, experience cognitive detriments (Trivedi & Greer, 2014)'. 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)'.Most patientssuffering 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 andmaintainspsychosocial 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)'0•

In an emerging economy like Pakistan, there is a growing need for cognitively skilled labour. Patients with MOD and cognitive dysfunction are at a disadvantage and may not receive the same employment opportunities.Giventhe growingnumber ofpeoplenow beingdiagnosed withdepression,alargeproportionof thepopulation may essentially, become obsolete.Cognitive impairmentsunderlying

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

Studies investigating depression and cognitive dysfunction, particularly in Pakistan arerare 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 andfunctional 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 patientssuffering fromMDD.

1. To explore the association between severity of depression and perceivedcognitivedysfunction.
2. 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 withmore than35investigators 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,bothmale and female, attending outpatient clinicsand diagnosed with an active episode of major depression using ICD-10 criteria, were selected using convenientsampling.

Patients were excluded if they had a present diagnosis or past medical history of schizophrenia,bipolardisorder, dementiaor 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, cerebrovascularaccident etc.) were alsoexcluded.

# 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)" (Busner and Targum 2007).CGI-Sis a standardised assessment tool for rating severity of an illness on a 7 pointsscale,where1Indicatesnormalhealth and 7 indicatesextreme 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 eachitem scored from 0 (not at all) to 3 (nearly every day).Total

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

***Perceived Deficits Questionnaire (PDQ):*** Cognitive dysfunction was assessed using perceived deficits questionnaire (PDQ- Lam et al., 2018)". 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 poorercognitive 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 eachoft he 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 patientsencountered,haveaffected theirlives.

# Procedure

Ethical approval for the study was obtained from the Institutional Research and Ethics Forum (!REF), Rawalpindi Medical University and Allied Hospitals, Rawalpindi, Pakistan. Signed informed consent was obtained from allparticipantsfor participation inthestudy.

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 truediagnosis of depression the participants first rated themselves using a PHQ-9 test and then were rated by research assistants on the (GI-Severity scale.Patients who scoredhigher than a 5 on the CGIscale 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 wrotedown their responses. All data wascollated andanalysed 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

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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 findout interrelationshipsand 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 wastreatedas.

**RESULTS**

Patientshad a meanageof 35.48 ± 11.07 (121patients wereoverthe 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 femalesand 36.3

%were housewives(see table1).

#### Table *1*

Descriptive data of participants

|  |  |
| --- | --- |
| **Treatment status** | **N(¾)** |
| **No** | 1894 (73) |
| **Yes** | 705 (27) |
| Receiving psycho1herapy | 288 (II.I) |
| Receiving phannacotherapy | 630 (24.2) |
| TCAs | 50 (1.9) |
| SSRls | 583 (22.4) |
| SNRI | 54 (2.1) |
| **Education** | **N(¾)** |
| Noeducation | 632 (24.3) |
| Primary | 283 (10.9) |
| Middle | 234 (9) |
| Matric | 485(18.7) |
| Intermediate | 400 (15.4) |
| University | *5*I 4 ( 19.8) |
| Other | 43 (1.7) |
| Missing | 8 (0.3) |
| **History of previous depressive episode(N=691) (Mean- 2.4, *S.D=J.****7)* | **N(¾)** |
| One episode | 277 (40) |
| Two episodes | 231 {33.42) |
| Three episodes | 183(26.4) |
| **Duration of current episode (N"'2593)** | **N(¾)** |
| Less than one week | 36 (14) |
| One-twu weeks | 220 (8.5) |
| Three-four weeks | 473 (18.2) |
| Five-eight weeks | 568 (21.9) |
| More than eight weeks | 1296 (49.9) |

*Many patienls were on multi-model treatment including p ychotherapy and pharmacotherapy with more than one class of'ami-depressa111s. hence, !he treMme,u m1mber.1· ,ton'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 (o/o)** |
| Punjab (J0) | 1442 (55.6%) |
| Baluchistan (I) | 315 (14.2%) |
| Simi (4) | 322 (13.5%) |
| Khyber Pakhtunkhwa (3) | 398 (12.4%) |
| Azad Jammu and Kashmir (1) | 120(12.1%) |
| Total (19) | 2599(100%) |

Table 3 showedthe correlationalanalysisconducted.Results showed a positive relationship between depression severity, perceived cognitive dysfunction and functional disability, as shown by Pearson's correlationscoefficients.

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 shownby Pearson's correlation coefficients.

**Table 3**

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

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PRQ-9** | **PDQ** | **WHODAS-12** |
| PHQ-9 | - | .619\*\* | .663\*\* |
| PDQ |  |  | .700\*\* |
| WHODAS-12 |  |  | - |

\*\*, *Correlation is signif,ca111at the 0.OJ level (2-railed)*

Table 4 shows that the majority of the participants reported moderate (36.4%) to severe (33.4%) depression as assessed by PHQ

(total PHQ-9score [mean± SD]:17.44 ±4.64).

#### Table4

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

|  |  |
| --- | --- |
| **PHQ-9 Categories** | /{¾) |
| Nodepression (0-4) | . |
| Mild depression (5-9) | 19 (7%) |
| Moderate depression ( I 0-14) | 769 (29.4%) |
| Moderately severe depression (15-19) | 952(36.4%) |
| Severe depression (20-27) | 873 (33.4%) |

Patients reporteda meantotalPDQ-D score of 40.41 ± 15.064; 70.7% (1850/2599) of the study population hadaPDQ-D score ;;;,32. PDQ-D scorerange(mean± SD) by quartileasseen in Table5.

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#### Table 5

Patient's PDQ scores

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Our study highlights that more than two third patients who receive a diagnosis of MOD harbor cognitive dysfunction. By examining participants with both PHQ-9 and CGl(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 thisdisabling correlate of depression. This is even more crucial when effective pharmacological and

|  |  |
| --- | --- |
| 1s1quartile (n=62) | 0-9(5.26±2.717) |
| 2nd quarl.ilc (11=163) | 10-19 (15.28 ± 2.849) |
| 3rd quartile (n=532) | 20-31 (26.75 ± 3.239) |
| 4th quartile (n=l850) | 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 wereyounger (aged 18-30,aged31-42,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 (PHO, 18.44 ± 4.397) (F (3, 2294)=3.037, p=0.028], living in

small towns (PHO, 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 (PHO, 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 higherfunctional disability scoresfor patients who:wereequal ormore than55 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 anepisode of Major depression as well as to explore the associations between depression severity, perceived cognitivedysfunction and functional disability.Thisstudyconducted 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 shownthat94% patientsin hisstudy experienced cognitive dysfunction". A relatively higher proportion in his study endorses that cognitive dysfunction in patients of depression is almost aconstant 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 populaces.

nonpharmacological interventions are available for the management of cognitive dysfunctions. The existing ignorance amongst clinicians is therefore bound to increase the existing treatment gapin 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 reported". Their study wasconducted in ahospital-based sample from atertiary care facility from Karachi,(amegapolis 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) havealso shown the presence of such a correlation•. This observation gains significance as when the three correlates are experienced simultaneouslythey are bound to makeeach other worseand have a qualitatively negative impact on the patient's mental state. Left unaddressed, this may have long term implications on prognosis.

Thisstudy 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, whichisin linewith previousresearch conducted investigating these factors (Ladin, 2008; Miech & Shanahan, 2000; Pearlin, 1975; Boughton, 2011)"·". These findings suggest the need for future treatment plansand interventionsto focus on cognitive dysfunction asmuchason depressive symptoms.Theneed to do so isevenhigher 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 MOD.The study was the first of itskind to assess and describe cognitive dysfunction in patients suffering fromMODin Pakistan and added to the limited evidence base in this area. The study allowed valuable insight into how cognitive dysfunction relatesto depression severityand everyday functioning of patients.

## LIMITATIONS OFTHESTUDY

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

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interpretationsand inferencesof causality due to the lack of controls and methodological constraints in the study. Dueto the studybeing 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 studyuseda measure of perceived cognitive dysfunction but measuresof specificcognitive declineand regression analysis were not conducted. This limits the predictive validity ofour study.

### CONCLUSION AND CLINICAL IMPLICATIONS

This study is a step towards early identification, management and possible prevention of cognitive dysfunction in patients of MOD. 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 illnesstrajectory in patients withMDD. Future studies should focus on interventions to reduce cognitive deficits in hopes to improvehealth outcomes and illness trajectory in patients **with** MOD. Future studies should also use more potent measures of cognitive dysfunction and undertake regression analyses of the possible risk factorsthatcontributetowards cognitive declinein patients of MDD.

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### CONFLICT OF INTEREST

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