Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 9 (2025)

Online ISSN 3007-3197
Print ISSN 3007-3189

http://amresearchreview.com/index.php/Journal/about

Cognitive Behavior Therapy (CBT), Islam-Based Interventions (IBIs) and Pharmacotherapy (PTh) for Patients with Major Depressive Disorder-Mild (MDD-m): A Randomized Control Trial

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ABSTRACT

Present study aims to investigate the effectiveness of pharmacotherapy (PTh), cognitive behaviour therapy (CBT), and Islam-based interventions (IBIs) to treat symptoms severity of patients MDD-m. This RCT was completed from December 20, 2020, to October 31, 2021, at different hospitals in Faisalabad, Pakistan. A total of 287 were approached, 204 were assessed for eligibility, and 158 met the inclusion criteria, including males 71(44.94%) and females 87(55.06%) with the age range of 22 to 46 years. Findings reported all treatment conditions (i.e. PTh, CBT, & IBIs) significantly reduced depressive symptoms severity ($p<.001$) and negative mood affects ($p<.001$) and significantly improved the level of memory ($p<.001$), reasoning ability ($p<.001$), decision-making skills ($p<.001$), self-esteem ($p<.001$), and wellbeing ($p<.001$) as compared to the waitlist-control group. Multiple groups comparison reported significant differences across the groups. Moreover, significant symptoms change was observed after treatment which indicates all treatment conditions produced outstanding outcomes. It is concluded that all the treatment conditions substantially decreased the depressive symptoms and negative mood as compared to waitlist-control group. These treatment condition significantly improved the quality of life, memory and decision-making skills in daily life functioning. This indicates PTh, CBT and IBIs are reliable and evidence-based practices to treat MDD-m.

Keywords: Major Depressive Disorder-Mild, Cognitive Behaviour Therapy, Islamic Intervention, Pharmacotherapy, Memory, Decision-Making Skills, Self-Esteem

INTRODUCTION

Major depressive disorder (MDD) is a common psychiatric disorder rising high worldwide and causing economic burden, mortality and morbidity [1,2]. According to an estimation, the lifetime prevalence of major depressive disorder is 2 to 21%, with a lower ratio in Asian

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Volume 3, Issue 9 (2025)

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countries and higher in European countries [3]. The global prevalence of major depressive disorder is more common among older adults, 13.3%, and women, 11.9% [4]. MDD prevalence in the United States is approximately 7% and almost 12% to 16% in Western communities [5]. It affects females disproportionately, like 1.5 to 3 times higher than men, and its prevalence among in-door patients is relatively higher, estimated at almost 29.4% [6]. In Pakistan, the prevalence of depressive symptoms is estimated at 27.4% among the sample [7].

The diagnostic features of MDD are the combination of core symptoms, i.e., suicidal ideation and lack of interest in activities and primary symptoms, i.e., sleep disturbance, psychomotor agitation, poor appetite, discouraged disposition, weight loss, and fatigue (APA, 2013). Severity in symptoms increases suicidal ideation [8], hopelessness [9], low mood [10], and functional impairment [11]. In a primary care setting, to address the clinical symptoms, historically, the major focus is on pharmacotherapy (Prescott & White, 2017). Currently, various psychotherapies have been approved as evidence-based treatment i.e. cognitive behaviour therapy[12]. Islam-based therapy has also gained popularity as an evidence-based intervention to deal with depressive symptoms with various positive outcomes [13]. When patients do not respond to pharmacotherapy and do not improve daily functions are usually referred to long-term therapies with intensive treatment services. Evidence-based psychotherapies and Islam-based therapies help to reduce stigma and psychological barriers and increase their availability and accessibility [14,15]. Pharmacotherapy (PTh) quickly addresses depressive symptoms and provides significant relief to a person, but it cannot provide problem root causes and skill training. Some patients improve through medications. Suicidal potential, mood stability and sleep hygiene can be effectively managed using rapidly acting antidepressant therapies [16]. Some patients respond differently to medication and experience severe side effects, and sometimes those who have the problem with cognitive terms prefer psychotherapies [17,18].

CBT is an evidence-based, problem-focused therapy [19] and time-limited, usually producing satisfactory results in 10-12 therapeutic sessions [20]. CBT is recommended therapy for MDD with several pieces of evidence that diminish the uneasiness of social interaction and help the person to overcome emotional disturbance [21]. It effectively works face-to-face, applying a specific agenda [22] and goal setting [18]. CBT provides

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psychoeducation, cognitive restructuring, identifying, evaluating and responding to automatic thoughts, emotions and beliefs using various techniques and homework assignments, yielding positive outcomes [23]. It provides self-help [24], enhances memory [25] and has no side-effects [17]. CBT produces almost 75% positive outcomes in the treatment of MDD [26].

Islam-based therapy is another evidence-based modality that has produced significant results for depressive symptoms [27]. Offering prayers five times a day is a healthy exercise to improve hygiene, social interaction, and the opportunity to communicate with each other [28]. Recitation of the Holy Quran and its spiritual practices increase the relaxation of the mind [29]. It is more or less like psychotherapy. It was designed to have different agendas, i.e., psychoeducation, motivation, positive perception, stress management, fully functioning, decision-making and problem-solving, effective relationship, self-growth, and lapse and relapse prevention. It is a convenient treatment approach to easily practice, understand, and implement to reduce depressive symptoms and improve the level of well-being, self-esteem, decision-making, memory, and abstract reasoning [30,31].

In Pakistan, the general public is more familiar with pharmacotherapy and less familiar with psychological treatment. Therefore, they rush to the primary care service provider, get medication and experience quick symptoms relief. Some people practice religious remedies to manage depressive symptoms, and it seems effective when patients eagerly involve themselves in activities and remain focused on them. But we have no scientific evidence of how effective these interventions have produced substantial outcomes because research evidence lakes. The present study aimed to investigate the impact of pharmacotherapy, cognitive behavior therapy, and Islamic-based intervention in treating major depressive disorder-mild. We focus on the patient's severity level of depressive symptoms, memory, reasoning ability, decision-making skills, self-esteem, and well-being in the treatment process by reducing the time between the first diagnosis and the subsequent treatment, thereby improving treatment outcomes.

METHODS

Design

The current randomized control trial compares the effectiveness of three different interventions, i.e. pharmacotherapy (PTh), cognitive behaviour therapy (CBT) and Islam-

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based interventions (IBIs) in the outpatient setting with a duration of 16-20 weeks. Outcome measures were obtained at the baseline and post-interventions. The study protocol was approved by the Institutional Review Board (IRB), Government College University, and Faisalabad, Pakistan (i.e., Ref.No.GCUF/ERC/2076).

Participants

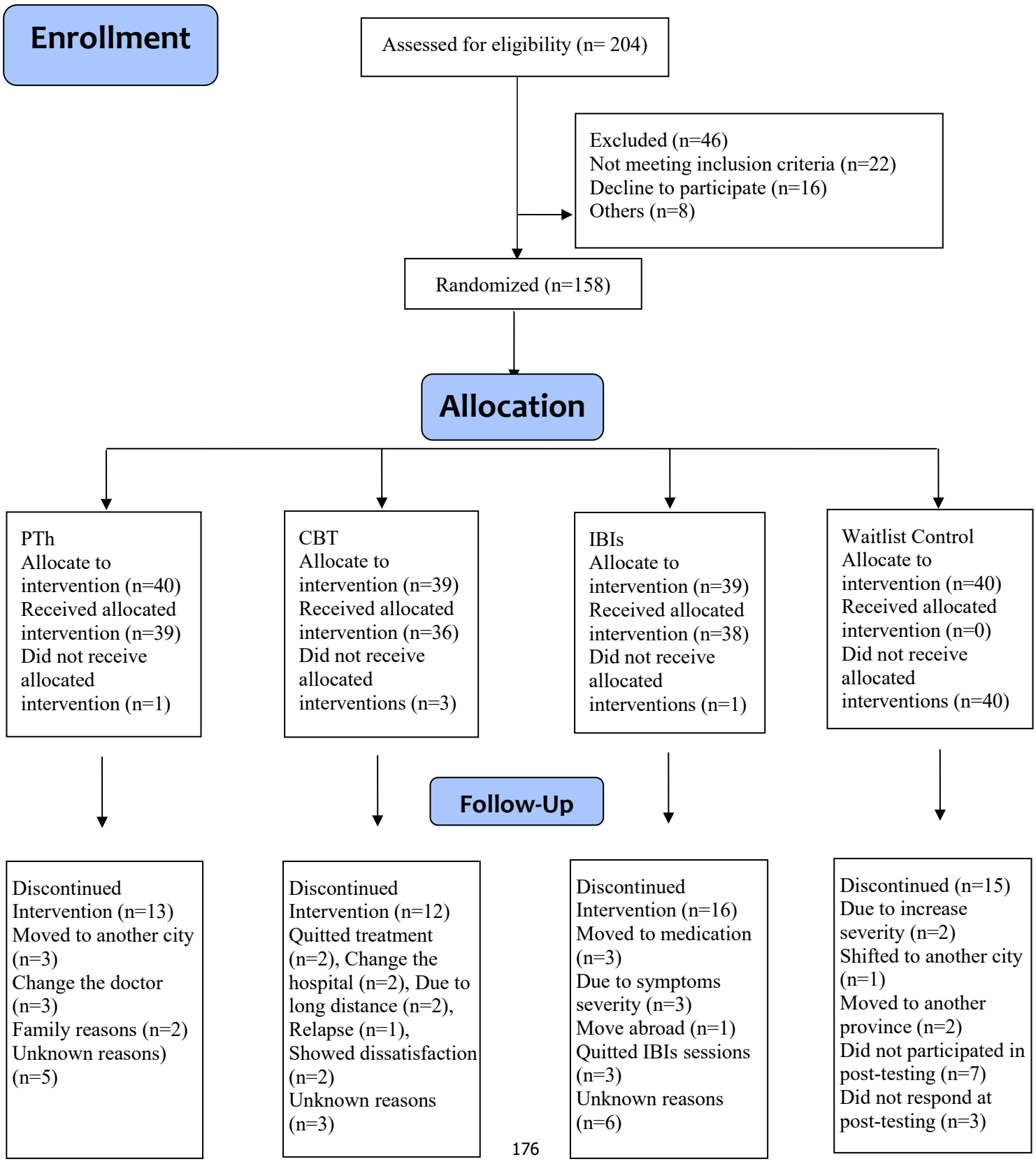
Participants were taken from different psychiatric hospitals and primary care settings from December 20, 2020, to October 31, 2021. Participants who met the primary diagnostic criteria of major depressive disorder-mild were included (DSM-V, APA, 2013). Participants were differentiated through screening tools, differential diagnoses, and possible comorbidities were checked. Participants excluded have moderate severity, availing of inpatient facility, with multiple episodes, chronic patients (> 6 months duration of illness), medical comorbidity, or any physical and intellectual disability. Both genders with single and married status were included. Participants' age range was 22 to 46 years (M±SD=25.24±4.12).

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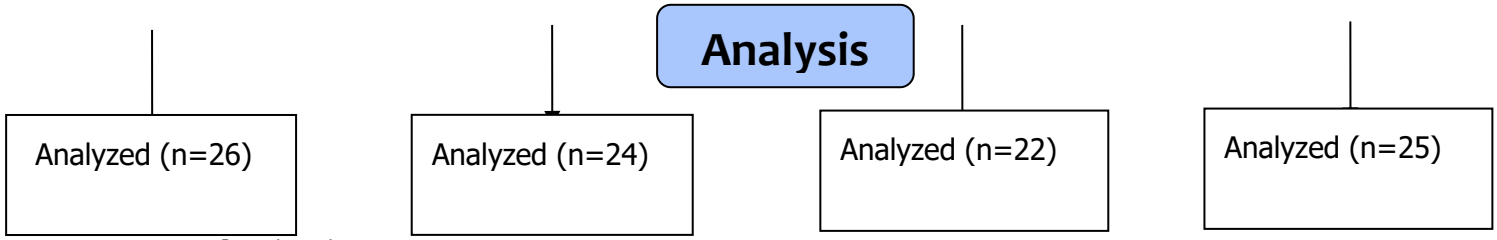
Figure 1: Flow Diagram of Patients with Major Depressive Disorder-Mild (MDD-m)



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Randomization

Initially, the participants were assessed for eligibility criteria. The eligible participants (N=158) were allocated to four groups through randomization. A total of 204 participants assessed for eligibility and 46 participants were excluded. The eligible participants were allocated to PTh, CBT, IBIs, and waitlist control.

Measures

Patient Health Questionnaire (PHQ-9): The PHQ-9 [32] Urdu version was used [33]. The PHQ-9 is a self-report measure that assesses depressive symptoms in patients for the past two weeks. Each item on the scale is evaluated on a 4-point scale from *not at all* (0) to *nearly every day* (3). The PHQ-9 also provides symptom severity, i.e., minimal, mild, and moderate-severe.

ICP Subjective Well-Being Scale (ICP-SWS): The ICP-SWS was used [34]. The ICP-SWS is comprised of 29 items with three domains, namely positive affect (PA), negative affect (NA), and life satisfaction (LS). PA and NA domains contain 12 items each, and the LS domain consists of 5 items. Each item is scored on a 5-point Likert scale. The scale has good psychometric properties, such as Cronbach's alpha for PA (.84), NA (.85), and LS (.81), with reasonable reliability estimations of 0.77, 0.73, and 0.83, respectively.

Digit-Span Subtest (DSS): The Digit-Span is the verbal subtest of WAIS-III [35] designed to assess subjects' working memory. The DSS is comprised of two subsections; such as Digits Forward and Digits Backward. Each subsection consisted of eight items. The DSS was administered with standard instructions. The average reliability coefficient for DSS is calculated at 0.91[35].

Standard Progressive Matrices (SPM): The SPM is a test of intelligence that measures an aspect of abstract reasoning through nonverbal tasks [36]. The SPM consists of 60 nonverbal tasks with five sets (i.e., ABCDE). Initially, the SPM provides raw scores, converting them according to standard scoring procedures (Raven, 1983). Finally, SPM provides intellectual capacities from *intellectually superior* to *intellectually defective*. The SPM

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has good reliability of 0.90 and a validity estimation of 0.86 (Raven et al., 1983). Some studies have shown that SPM is a very reliable measure.

Rosenberg Self-Esteem Scale (RSES): The Urdu version of RSES is ten items self-report measure designed to assess an individual's self-esteem [37]. It is 4 points Likert-type scale from *strongly agree* (3) to *strongly disagree* (0). High scores indicate a higher degree of self-esteem, and lower scores indicate low self-esteem. The RSES reliability estimation is 0.87.

Decision-Making Questionnaire (DMQ): The DMQ is a 21 items scale that was sued. The DMQ includes seven domains: control, thoroughness, instinctiveness, social resistance, hesitancy, perfectionism, and idealism [38]. Each statement is scored on 6 points Likert-type scale from never or infrequently to very often or permanently. A high score reflects the power to decide, whereas a low score indicates low decision-making skills.

Interventions

Pharmacotherapy (PTh): PTh is an effective treatment that has produced substantial outcomes [39]. Antidepressants effectively treated patients with a depressed mood and suicidal potential [40]. Antidepressant drugs are primarily used to treat MDD-m, focusing on managing patients' depressive symptoms and enabling them to perform better life functions [41]. Some other evidence suggests that antidepressants manage and overcome some pathways that are more relevant to developing MDD-m, such a immune-inflammatory tracks [42], peripheral levels [43], and frontal-limbic networks (Brakowski et al., 2017). The PTh treatment for MDD-m is a viable treatment choice, but studies have reported that 60% of patients discontinued medication due to severe side effects [14]. After psychological assessment and diagnosis, patients were referred to a psychiatrist for medications. During the PTh, medicine was given to each participant according to symptoms severity, and follow-up sessions were adequately maintained.

Cognitive behaviour therapy (CBT): CBT has produced effective outcomes with MDD-m [19]. CBT is evidence-based [45], time-limited [46] and problem-focused [47]. This study practiced CBT after a proper treatment protocol designed with specific agendas and frequency of sessions. Our target agendas were psychoeducation, motivation, cognitive conceptualization, stress management, problem-solving, behavioural management, decision-making skills, effective relationship and lapse, and relapse prevention. This topic was selected from two primary sources, i.e., Cognitive Behavior Therapy-Basic and Beyond [48],

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and material freely available from the mind's website https://www.mind.org.uk/information-support/types-of-mental-health-problems/ in which therapists can get cognitive behaviour therapy for their patients with depression. Each session was conducted in a one-on-one setting with each patient. Session frequency was planned as one session per week. Moreover, during these sessions, family members of the patients were made aware of the patient's nature of the illness [49]. A few recommendations were given to them regarding how they can effectively deal with the patients at home (see Supplementary file 1).

Islamic-based interventions (IBIs): The IBIs significantly address depressive symptoms [27]. Surah Al-Rahman recitation, translation and briefly described to the client works as a relaxation exercise and decreases mood-related symptoms[30]. When recited and listened to with more profound concentration, Quranic verses heal sadness [50]. The IBIs comprised 8 -10 sessions with specific agendas (i.e., psychoeducation, motivation, positive perception, stress management, problem-solving, fully functioning, decision making and problem-solving, effective relationship, self-growth, and lapse and relapse prevention). Each session consisted of 40 to 60 minutes [51]. The IBIs' major interventions were planned, including different activities (i.e., Namaz), relaxation exercises (i.e., listening to Surah AlRehman), and religious practices at the same intervals. The main target of IBIs was to reduce depressive symptoms and improve the level of wellbeing, self-esteem, decision-making, memory, and abstract reasoning [30,31] (see Supplementary file 2).

Procedure

All procedures are authorized by the Institutional Review Board (IRB) of Government College University, Faisalabad. We assigned the participants to treatments using block randomization to ensure the numbers allocated to each group were balanced. Participants were recruited from different psychiatric clinics, hospitals and primary care settings. The therapist briefly explained to the subjects about the study. Participants were included; they can read, write and understand. Initially, the therapist described the confidentiality, and a consent form was given to the participants. After getting written informed consent, the initial assessment process was inducted. Patients who met the diagnostic criteria were randomly assigned to treatment conditions (i.e., Med, CBT& IBIs) and waitlist-control. Measurement scales were used to compare the pre-and post-outcomes (i.e., PHQ-9, SWS,

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Volume 3, Issue 9 (2025)

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Print ISSN 3007-3189

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DSS, SPM, SES, DMQ).

Statistical Analysis

Descriptive statistics (Mean &SD) were used to calculate sample demographic characteristics. Group characteristics were compared at pretest using chi-square and one-way ANOVA to compare categorical and continuous variables. A mixed ANOVA statistic was used for the assessment time (pre- versus post-test) to evaluate the effects and benefits of the interventions (between-group effects). Frequency distribution statistics were used to find out the depression severity. Bonferroni test was used to compare the groups on the scale of PHQ-9, SWS, DSS, SPM, SES, and DMQ. An alpha of .05 was used for all analyses, and *p*-values <.05 were submitted to Bonferroni correction using IBM SPSS Statistics (Version 26).

RESULTS

Recruitment and Attrition

A total of N=287 patients were approached. 83(28.92%) participants did not provide informed consent, 46(16.03%) participants did not complete the initial screening, 204(71.08%) were assessed for eligibility, and 158(55.05%) met the study inclusion and exclusion criteria. The total attrition rate was 97(61.39%), and 61(38.61%) were excluded for a due variety of reasons (Fig. 1).

Sample Characteristics And Baselines Assessment

The sample characteristics are described in the Table 1. The chi-square and one-way ANOVA analyses reveal the in-significant differences among PTh, CBT, IBIs and Waitlist-control on gender (X^2=.254, p>.968), marital status (X^2=.830, p >.842), education (X^2=2.059 p >.914), referral source (X^2=2.430, p >.488), duration of illness (X^2=.3.570, p >.735), family system (X^2=.2.024, p >.890), age (F=.550, p>.650) and monthly income (F=.090, p>.965). Furthermore, group comparisons were investigated among the treatment variables among groups using one-way ANOVA. The baselines findings indicate insignificant differences among four treatment groups and waitlist-control on PHQ-9 (F=.381, p>.767); PAS (F=.651, p>.584), NAS (F= 1.505, p>.215), LSS (F=1.107, p>.348), SWB-T (F=.328, p<.805), DSS (F=.063, p>.979), SPM (F=.635, p>.593), SES (F=.607, p>.612), DMQ (F= .177, p>.912).

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Table 1: ***Baselines Sample Characteristics of the Participants***

Variables Characteristics	Category	N	Groups PTh	CBT	IBIs	Waitlist control	X^2/F	p
N Allocated		204	40(25.3%)	39(24.7%)	39(24.7%)	40(25.3%)		
N Dropout		61	14(22.95%)	15(24.59%)	17(27.87%)	15(24.59%)		
N final		97	26(26.81%)	24(24.74%)	22(22.68%)	25(25.74%)		
Age, M(SD)		158	30.85(6.91)	29.90(6.20)	28.95(7.14%)	30.27(6.74)	.550	.650
Monthly Income M(SD)		118	84325.0 (35184.78)	85102.57 (49334.41)	88871.80 (44233.34)	87250.0 (43149.56)	.090	.965
Gender	Female	87	23(26.44%)	22(25.29%)	21(24.14%)	21(24.14%)	.254	.968
	Male	71	17(23.95%)	17(23.95%)	18(25.35%)	19(26.76%)		
Marital Status	Single	114	31(27.19%)	28(24.56%)	27(23.68%)	28(24.56%)	.830	.842
	Married	44	9(20.46%)	11(25.00%)	12(27.28%)	12(27.28%)		
Edu.	Intermediate	58	11(18.96%)	16(27.59%)	15(25.86%)	16(27.59%)	2.059	.914
	Graduate	46	13(28.27%)	11(23.91%)	11(23.91%)	11(23.91%)		
	Post-G	54	16(29.63%)	12(22.23%)	13(24.08%)	13(24.08%)		
Referral Source	Self-app.	72	14(19.45%)	19(26.39%)	19(26.39%)	20(27.78%)	2.430	.488
	Referred	86	26(30.23%)	20(23.26%)	20(23.26%)	20(23.26%)		
DOI	< 1 Months)	97	24(24.74%)	21(21.65%)	23(23.71%)	29(29.90%)	3.570	.735
	1-2 Months)	34	8(23.53%)	10(29.41%)	9(26.47%)	7(20.59%)		
	< 4 Months	27	8(29.63%)	8(29.63%)	7(25.93%)	4(14.82%)		
Family System	Nuclear	88	23(26.14%)	22(25.00%)	23(26.14%)	20(22.72%)	2.024	.890
	Joint	70	17(24.29%)	17(24.29%)	19(27.13%)	17(24.29%)		

Note: M(SD)= Mean (Standard Deviation); PTh= Pharmacotherapy; CBT: Cognitive Behavior Therapy; IBIs= Islam-based Interventions, Edu. = Education; Self-app.= Self-approached; Post- G = Post-graduate; DOI= Duration of illness;

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Online ISSN 3007-3197
Print ISSN 3007-3189

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Table 2: Mean (Standard Deviation) and Mixed-Design ANOVA of Clinical Scores During Pre- and Post-Test Interventions

	Groups														
	PTh		CBT		IBIs		WLC		Group x Time						
	Pretest	Post-Test	Pretest	Post-Test	Pretest	Post-Test	Pretest	Post-Test	Group		Time		Interaction		
	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	F	P	F	P	F	P	η_p^2
PHQ-9	0.31(1.13)	2.69(3.76)	9.71(2.29)	.63(4.45)	9.79(1.76)	.55(5.68)	20.12(1.24)	20.40(3.00)	48.41	.001	71.69	.001	37.25	.001	.745
PAS	6.27(3.94)	5.96(8.72)	5.75(7.21)	1.00(8.95)	6.19(5.67)	3.09(5.65)	25.24(4.76)	26.28(5.07)	26.77	.001	18.92	.001	51.80	.001	.774
NAS	4.85(3.36)	1.31(3.58)	5.84(5.32)	2.63(3.23)	3.23(5.76)	9.09(7.54)	35.08(4.41)	35.12(4.58)	32.84	.001	90.69	.001	85.38	.001	.864
LSS	0.88(2.13)	5.93(2.17)	0.46(2.77)	3.08(2.15)	1.77(2.73)	3.14(6.29)	10.72(2.27)	11.08(2.10)	42.42	.001	24.78	.001	49.37	.001	.777
DSS	.27(2.33)	3.08(1.85)	.63(2.61)	0.92(2.11)	.91(2.53)	6.73(3.62)	9.64(2.33)	10.08(2.45)	38.44	.001	54.48	.001	53.44	.001	.792
SPM	0.96(23.50)	2.31(20.31)	0.63(16.17)	2.08(18.71)	0.91(12.31)	0.22(23.48)	37.16(14.31)	37.60(14.51)	3.53	.001	7.23	.001	10.20	.001	.454
SES	2.50(2.94)	3.58(3.75)	2.25(2.59)	8.29(1.97)	2.09(2.23)	9.14(2.17)	12.12(1.90)	11.48(2.20)	20.54	.001	04.03	.001	31.55	.001	.528
THD	4.38(2.06)	5.69(3.72)	4.34(1.79)	7.58(4.59)	4.05(2.35)	7.14(1.73)	15.00(2.25)	14.85(1.97)	1.55	.208	1.15	.001	3.48	.019	.185
CND	2.69(1.55)	2.07(2.67)	3.13(1.78)	0.79(4.91)	3.50(1.95)	1.10(2.67)	13.16(2.34)	15.16(3.74)	31.03	.001	02.96	.001	25.86	.001	.525
HED	0.96(2.15)	1.07(1.63)	2.46(3.04)	1.38(1.58)	3.09(2.02)	1.22(1.69)	11.56(2.28)	11.84(2.04)	1.99	.119	.80	.011	4.23	.008	.068
SRD	.50(2.05)	0.19(3.34)	0.42(1.74)	3.63(2.50)	.64(2.61)	2.50(1.37)	9.28(2.09)	9.44(2.29)	12.23	.001	8.55	.001	5.59	.001	.235
PRD	.38(1.92)	.43(1.14)	.58(3.09)	0.42(2.21)	.27(2.47)	.88(2.04)	8.28(2.99)	9.48(3.07)	2.26	.086	9.61	.001	4.27	.001	.348
IDD	.66(1.77)	.31(1.29)	.71(0.55)	.25(1.48)	.73(1.16)	.00(1.27)	7.80(2.69)	7.64(2.22)	3.01	.034	6.67	.001	8.76	.001	.283

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IND	.73(1.32)	.85(1.26)	.29(1.61)	.96(1.33)	.14(1.88)	.95(1.33)	8.04(2.09)	8.60(1.96)	7.26	.001	6.61	.001	4.29	.007	.222
DMQ	6.69(4.22)	8.46(15.95)	6.92(8.65)	6.91(13.93)	6.50(6.17)	4.73(11.05)	67.12(7.44)	66.08(7.83)	24.58	.001	43.96	001	6.04	001	.608

Note: *=p<.05; ***=p<.001; η_p^2:Partial Squared Eta; PHQ-9=Patients Health Questionnaire; PAS=Positive Affect Scale; NAS=Negative Affect Scale; LSS=Life Satisfaction Scale; DSS=Digit Span Scale; SPM=Standard Progressive Matrices; SES=Self-Esteem Scale; THD=Thoroughness Domain; CND=Control Domain; HED=Hesitancy Domain; SRD=Social Resistance Domain; PRD=Perfectionism Domain; IDD=Idealism Domain; IND=Instinctiveness Domain; DMQ=Decision Making Questionnaire; PTh=Pharmacotherapy; CBT=Cognitive Behavior Therapy; IBIs=Islam-based Interventions; WLC: Waitlist-control

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Print ISSN 3007-3189
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The main effect on PHQ scores is statistically significant, sphericity assumed $F(1,93)=271.69$, $p<.001$, $\eta^2= .745$. This effect was qualified by a significant time x group interaction effect, sphericity assumed $F(3,93)=37.25$, $p<.001$, $\eta^2= .546$. The main effect on PAS, NAS and LSS scores is statistically significant i.e. $F(1,93)=318.92$, $p<.001$, $\eta^2= .774$; $F(1,93)=590.69$, $p<.001$, $\eta^2= .864$; $F(1,93)=324.78$, $p<.001$, $\eta^2= .777$. This effect was qualified by a significant time x group interaction effect, sphericity assumed i.e. $F(3,93)=51.80$, $p<.001$, $\eta^2= .626$; $F(3,93)=85.38$, $p<.001$, $\eta^2= .734$; $F(3,93)=49.37$, $p<.001$, $\eta^2= .614$. The main effect on DSS scores is statistically significant, sphericity assumed $F(1,93)=354.48$, $p<.001$, $\eta^2= .792$. This effect was qualified by a significant time x group interaction effect, sphericity assumed $F(3,93)=53.44$, $p<.001$, $\eta^2= .633$. The main effect on SPM and SES scores is statistically significant, sphericity assumed $F(1,93)=77.23$, $p<.001$, $\eta^2= .454$; $F(1,93)=104.03$, $p<.001$, $\eta^2= .528$ respectively. This effect was qualified by a significant time x group interaction effect, sphericity assumed $F(3,93)=10.20$, $p<.001$, $\eta^2= .247$; $F(3,93)=31.55$, $p<.001$, $\eta^2= .504$. The main effect on THD, CND, HED, SRD, PRD, IDD, IND and DMQ scores are statistically significant, sphericity assumed $F(1,93)=21.15$, $p<.001$, $\eta^2= .185$; $F(1,93)=102.96$, $p<.001$, $\eta^2= .525$; $F(1,93)=6.80$, $p<.011$, $\eta^2= ..068$; $F(1,93)=28.55$, $p<.001$, $\eta^2= .235$; $F(1,93)=49.61$, $p<.001$, $\eta^2= ..348$; $F(1,93)=36.67$, $p<.001$, $\eta^2= .283$; $F(1,93)=26.61$, $p<.001$, $\eta^2= .222$ & $F(1,93)=143.96$, $p<.001$, $\eta^2= .608$ respectively. This effect was qualified by a significant time x group interaction effect, sphericity assumed $F(3,93)=3.48$, $p<.001$, $\eta^2= .101$; $F(3,93)=25.86$, $p<.001$, $\eta^2= .455$; $F(3,93)=4.23$, $p<.001$, $\eta^2= .120$; $F(3,93)=5.59$, $p<.001$, $\eta^2= .153$; $F(3,93)=4.27$, $p<.001$, $\eta^2= .121$; $F(3,93)=8.76$, $p<.001$, $\eta^2= .220$; $F(3,93)=4.29$, $p<.001$, $\eta^2= .122$; $F(3,93)=46.04$, $p<.001$, $\eta^2= .598$ respectively (Table 2).

Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 9 (2025)

Online ISSN 3007-3197
Print ISSN 3007-3189

http://amresearchreview.com/index.php/Journal/about

Table 3: Results of Bonferroni Comparison Test

Variables	*(I) Groups Trials*	*(J) Groups Trials*	*Mean Difference (I-J)*	*Standard Error*	*P-Value*	*95% CI*	
						LB	*UB*
PHQ	PTh	CBT	2.833*	.638	<.001	1.113	4.554
	PTh	IBIs	3.091*	.653	<.001	1.330	4.852
	PTh	WLC	-3.760*	.632	<.001	-5.462	-2.058
	CBT	IBIs	.258	.665	>.980	-1.536	2.052
	CBT	WLC	-6.593*	.644	<.001	-8.330	-4.856
	IBIs	WLC	-6.851*	.659	<.001	-8.628	-5.074
PAS	PTh	CBT	-2.260	1.520	>.844	-6.358	1.839
	PTh	IBIs	-8.521*	1.556	<.001	-12.716	-4.326
	PTh	WLC	5.355*	1.504	<.004	1.299	9.411
	CBT	IBIs	-6.261*	1.585	<.001	-10.535	-1.987
	CBT	WLC	7.615*	1.535	<.001	3.477	11.753
	IBIs	WLC	13.876*	1.570	<.001	9.644	18.109
NAS	PTh	CBT	3.848*	1.159	<.008	.723	6.973
	PTh	IBIs	1.918	1.186	>.656	-1.280	5.116
	PTh	WLC	-7.023*	1.147	<.001	-10.115	-3.931
	CBT	IBIs	-1.930	1.209	>.682	-5.188	1.329
	CBT	WLC	-10.871*	1.170	<.001	-14.026	-7.716
	IBIs	WLC	8.941*	1.197	<.001	5.714	12.168
LSS	PTh	CBT	-3.367*	.650	<.001	-5.119	-1.615
	PTh	IBIs	-4.051*	.665	<.001	-5.844	-2.257
	PTh	WLC	2.504*	.643	<.001	.770	4.238
	CBT	IBIs	-.684	.678	>.991	-2.511	1.144
	CBT	WLC	5.871*	.656	<.001	4.102	7.640
	IBIs	WLC	6.555*	.671	<.001	4.745	8.364
SES	PTh	CBT	-2.232*	.558	<.001	-3.736	-.729
	PTh	IBIs	-2.575*	.571	<.001	-4.114	-1.037
	PTh	WLC	1.238	.552	>.163	-.249	2.726

Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 9 (2025)

Online ISSN 3007-3197
Print ISSN 3007-3189

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	CBT	IBIs	-.343	.581	>.890	-1.910	1.225
	CBT	WLC	3.471*	.563	<.001	1.953	4.989
	IBIs	WLC	3.814*	.576	<.001	2.261	5.366
DSS	PTh	CBT	-4.598*	.560	<.001	-6.107	-3.088
	PTh	IBIs	-2.645*	.573	<.001	-4.190	-1.100
	PTh	WLC	.813	.554	>.874	-.681	2.307
	CBT	IBIs	1.953*	.584	<.007	.378	3.527
	CBT	WLC	5.411*	.565	<.001	3.887	6.935
	IBIs	WLC	3.458*	.578	<.001	1.899	5.017
SPM	PTh	CBT	-4.720	4.771	>.986	-17.583	8.144
	PTh	IBIs	-3.934	4.883	>.999	-17.097	9.230
	PTh	WLC	9.255	4.722	>.318	-3.474	21.983
	CBT	IBIs	.786	4.975	>.898	-12.627	14.199
	CBT	WLC	13.974*	4.817	<.028	.988	26.960
	IBIs	WLC	13.188	4.928	>.053	-.096	26.472
DMQ	PTh	CBT	-14.340*	2.309	<.001	-20.564	-8.116
	PTh	IBIs	-13.037*	2.363	<.001	-19.406	-6.667
	PTh	WLC	.977	2.285	>.999	-5.182	7.136
	CBT	IBIs	1.303	2.407	>.999	-5.187	7.793
	CBT	WLC	15.317*	2.331	<.001	9.033	21.600
	IBIs	WLC	14.014*	2.384	<.001	7.586	20.441

Moverover, multiple comparisons using Bonferroni test indicated significant differences among all groups on PHQ. For example, significant difference between PTh with CBT (2.833, p<.001), IBIs (3.091, p<.001) and WLC (-3.760, p<.001), CBT with WLC (-6.593, p<001), and IBIs with WLC (-6.851, p>.001) were found and insignificant difference was found between CBT and IBIs (.665, p>.980). On PAS, significant difference of PTh with IBIs (-8.521, p<.001), and WLC (5.355, p<.001); significant difference between CBT with IBIs (-6.261, p<.001) and WLC (7.615, p<.001) and significant difference of IBIs with WLC (13.876, p<.001), while insignificant difference between PTh and CBT groups (-2.260, p>.844). Multiple group comparisons on NAS showed significant difference between PTh with CBT (3.848, p<.001) and WLC (-7.023, p<.001); significant difference between CBT and

Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 9 (2025)

Online ISSN 3007-3197
Print ISSN 3007-3189
http://amresearchreview.com/index.php/Journal/about

IBIs with WLC (-10.871, p<.001; 8.941, p<.001) and insignificant difference of IBIs with PTh and CBT (1.918, p>.656; -1.930, p>.682). On LSS, significant group comparisons of PTh with CBT (-3.367, p<.001), IBIs (-4.051, p<.001) and WLC (2.504, p<.001), significant difference of WLC with CBT (5.871, p<.001) and IBIs (6.555, p<.001) were found and insignificant difference between CBT and IBLs was found (-.684, p>.991). Similarly, on SES group present significant difference of PTh with CBT (-2.232, p<.001) and IBIs (-2.575, p<.001); significant difference of CBT and IBIs with WLC (3.471, p<.001 & 3.814, p<.001) and insignificant difference of PTh with WLC (1.238, >.163) and CBT with IBIs (-.343, p>.980). Group difference on DSS was found significant of PTh with CBT (-4.598, p<.001) and IBIs (-2.645, p<.001); CBT with IBIs (1.953, p<.001) and WLC (5.411, p<.001); IBIs with WLC (3.458, p<.001); whereas, insignificant difference PTh and WLC (.813, p>.874). On SPM significant group difference was found of CBT with WLC (13.974, p<.001) and insignificant difference of PTh with CBT (-4.720, p>.986), IBIs (-3.934 p>.999), and with WLC (9.255 p>.318) and IBIs with CBT (.786, p>.898) and WLC (13.188, p>.053). Furthermore, group difference on DMQ was found significantly different; such as PTh with CBT (-14.340, p<.001) and IBIs (-13.037, p<.001); WLC with CBT (-15.317, p<.001) and IBIs (-14.014, p<.001); whereas, insignificant difference of PTh and WLC (.977, p>.999) and CBT with IBIs (1.303, p>.999) was estimated (see Table 3).

Table 4: ***The Severity Of Depressive Symptoms After Medication, Cognitive Behaviour Therapy, And Islamic Interventions With MDD-m***

Variables	PTh	CBT	IBIs	Total
Symptoms fully treated	2(7.7%)	6(25.0%)	10(45.5%)	19(26.4%)
Symptoms sig decreased	3(11.5%)	14(58.3%)	6(27.3%)	21(29.2%)
Symptoms managed	15(57.7%)	1(4.2%)	3(13.6%)	18(25.0%)
Symptoms remain same	6(23.1%)	3(12.5%)	3(13.6%)	14(19.4%)

Note: PTh=Pharmacotherapy; CBT=Cognitive Behavior Therapy; IBIs=Islam-based Interventions

Findings reveal that after treatment interventions significant decrease in symptoms severity was found. Symptoms fully treated with medication 2(7.7%), CBT 6(25.0%)

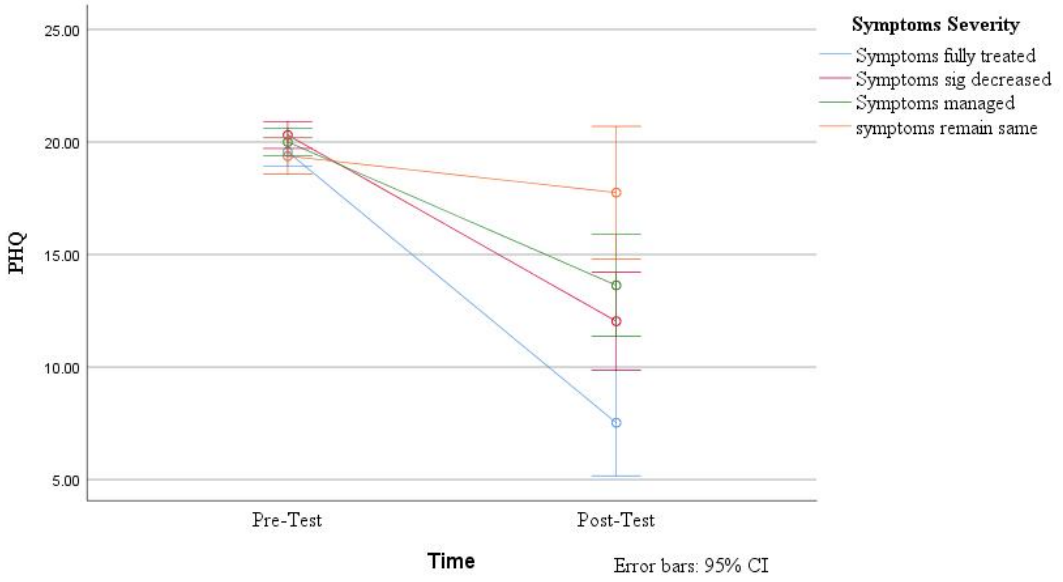
Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 9 (2025)

Online ISSN 3007-3197
Print ISSN 3007-3189

http://amresearchreview.com/index.php/Journal/about

and IBIs 10(45.5%). Symptoms significantly decreased with medication 3(11.5%), CBT 14(58.3%) and IBIs 6(27.3%). PTh was found to be an effective intervention to manage depressive symptoms 15(57.7%) as compared to CBT 1(4.2%) and IBI 3(13.6%). Depressive symptoms remain the same as among patients who used medication 6(23.1%), CBT 3(12.5%), and IBIs 3(13.6%), respectively (see Table 4).

Figure 2: Patients' symptoms severity after pharmacotherapy, cognitive behavior therapy, and Islamic-based interventions on PHQ



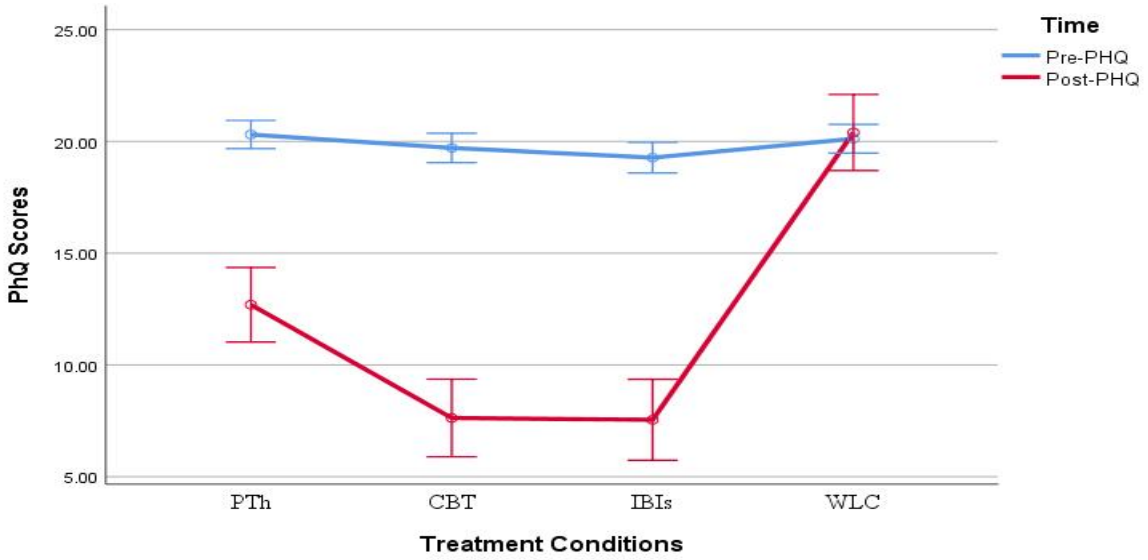
Results reported depressive symptoms severity significantly reduced on PHQ after PTh, CBT, and IBIs among patients with MDD-m. Pre-and post-test analysis indicates a substantial change in depressive symptoms. For example, a maximum of patients perceived no signs after treatment. Some participants observed a significant decrease in depressive symptoms, some were able to manage their symptoms, and others perceived the severity of the same symptoms (see Figure 2).

Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 9 (2025)

Online ISSN 3007-3197
Print ISSN 3007-3189

http://amresearchreview.com/index.php/Journal/about

Fig 3: Pre and Post-Scores of PHQ-9 on PTh, CBT, IBIs, and WLC among Patients with MDD-m



Note: PHQ-9=Patients Health Questionnaire; PTh=Pharmacotherapy; CBT=Cognitive Behavior Therapy; IBIs=Islam-based Interventions; WLC: Waitlist-control

Further findings reported CBT reduced the severity of depressive symptoms in all the treatment groups while the severity of the symptoms remain same among the control group. Moreover, CBT and IBIs reduced the symptoms severity as compared to PTh. Overall findings reveal that PTh, CBT and IBIs are the reliable treatment interventions to reduce the severity of MDD-m (see Figure 3).

DISCUSSION

Our findings reveal that PTh, CBT, and IBIs were found potential treatment interventions to reduce the depression severity among patients with mild-major depressive disorders. Similarly, PTh an antidepressant-based therapy, CBT, and IBIs substantially reduce the depression symptoms severity and improved the patients quality of life which can be assess through waitlist-control group [52]. Pakistan's first randomized clinical trial evaluated three treatment group and waitlist control supported and consistent with the previous outcomes to treat major depressive disorder (Asghar, et al., 2021). The score means difference on the PHQ scale indicates that PTh, CBT and IBIs effectively address the severity, negative mood affects, and emotional disturbance due to psychiatric symptoms [54].

Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 9 (2025)

Online ISSN 3007-3197
Print ISSN 3007-3189
http://amresearchreview.com/index.php/Journal/about

Some other factors like; perceiving pharmacotherapy as good with minimal side effects enhance patients' positive attitude and willingness to continue treatment. Moreover, patients respond positively to CBT because CBT-based interventions help the patients to psychoeducation, motivation, and develop a better understanding to overcome negative thoughts, emotions, and beliefs [55]. Islamic interventions worked effectively because of patients' orientation and religious practices. They were familiar with them. When they were taught this way, the easy-to-understand concept brought substantial improvement in depressive patients [56].

Post-testing outcomes reflect that CBT effectively helped the patients change negative cognitions into positive ones, which significantly reduced depressive symptoms[57]. Similarly, IBIs also effectively provided psychoeducation and increased motivation levels while the patients on medication were found to be low motivated [58]. CBT and Islamic intervention achieve enduring effects because both interventions increase psychological flexibility and reduce depressive symptoms [59]. Our data support that CBT and IBIs are effective interventions and can be the first treatment for depression [60]. Medication could be the second treatment choice at an early stage of depression because patients have a good understanding and fewer behavioural problems [61].

Further analysis reveals that IBIs significantly improved the level of positive affect in patients. CBT and IBIs enormously helped the person to manage positive (i.e., happy, active, fresh, successful, hope-full, appreciated, love & proud) and negative (i.e., hopeless, irritated, sad, guilty, anger, loneliness, restlessness & frightened) emotions for better psychological wellbeing [62]. On the other hand, CBT and IBIs equally reduce negative affect and enhance life satisfaction in depressive patients. Still, PTh was a less effective treatment approach [63].

Other findings showed that CBT was a more effective intervention than PTh and IBIs to boost memory, reflecting CBT is more targeted to cognitive resources; therefore, it is found more helpful to improve memory. Furthermore, PTh and IBIs were also found to work on memory significantly different. PTh was found less effective in improving the ability of decision-making. In contrast, CBT and IBIs were found to be more effective treatment modalities to enhance decision-making

Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 9 (2025)

Online ISSN 3007-3197
Print ISSN 3007-3189
http://amresearchreview.com/index.php/Journal/about

ability among patients with MDD-m. After treatment, patients with MDD-m who got CBT and Islamic intervention showed a significant difference in their abstract reasoning. Those who received drug therapy were weaker in boosting up their level of abstract reasoning[64]. Low self-esteem patients lead to major depressive disorder while accessing the pretesting. Patients with MDD-m feel dissatisfied, have self-negative thoughts, feel less confident than others, and have self-related negative vibes come to mind. There was a significant difference in pre-and post-test scores who got CBT and IBIs showed a high level of self-esteem compared to those who received drug therapy [65].

The study findings indicate that level of depression was found to be mild at baseline screening which means untreated symptoms lead to severe indication, particularly in the area of consideration [66]. Untreated symptoms increase cognitive shortfalls and reduce working memory, memory encoding and review[56]. In this way, early management of techniques and appropriate depression treatment should be started to diminish the uneasy psychological issue of the patient [67]. Among the sample, it is seen that CBT and IBIs provided understanding and skills to overcome depressive symptoms, and PTh remained successful in reducing symptoms severity at the superficial level [68]. CBT worked effectively to restructure the cognitive beliefs, and patients also developed a better understanding of IBIs because they were a bit familiar with religious orientation and practices [69].

Our results indicate that patients with MDD-m reported healthier outcomes to address depressive symptoms who received CBT and IBIs than PTh [46]. Findings are somewhat relevant to Zhang et al. [18], who also found a significant impact of CBT on depressive disorders. The CBT and IBIs emphasize psychoeducational demonstration and a patient's active interest in homework, whereas mental and behavioural techniques aim to change the belief system [31]. The PTh remained helpful to reduce symptoms severity and failed to develop understanding and psychoeducation [70]. Thus, CBT and IBIs significantly reduced the depressive symptoms and improved the degree of memory, reasoning ability, decision-making skills [71], and self-esteem [72] as compared to medication (See Supplementary file 3). At the termination stage, patients were educated about lapse

Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 9 (2025)

Online ISSN 3007-3197
Print ISSN 3007-3189
http://amresearchreview.com/index.php/Journal/about

and relapse prevention [31].

CONCLUSION

It is concluded that PTh, CBT, and IBIs significantly reduce the depressive symptoms among patients with major depressive disorder-mild (MDD-m). Moreover, treatment conditions substantially improved memory, reasoning ability, decision-making skills, and self-esteem. A significant decrease in depressive symptoms was seen. Results also supported the patients' maximum benefits and got relief in symptoms of severity and quality of life from all treatment conditions (i.e. PTh, CBT, & IBIs). As evidence have been reported PTh and CBT are effectively and widely used interventions, and IBIs also emerged as an evidence-based therapy which created effective and fascinating trend like PTh and CBT. All the interventions provided subsequent relief to patients from primary and secondary symptoms throughout the treatment and follow-up phase.

LIMITATIONS OF THE STUDY

In Pakistan, psychiatric problems are increasing due to limited treatment facilities and practitioners, and the most common issue is a lack of awareness. Most individuals still go to quacks and non-professionals for help and receive remedies from them, which usually do not work professionally. Therefore, the majority believe that psychiatric problems are untreatable and there is no proper place for treatment. In some megacities in Pakistan, psychiatric hospitals and clinics are available but limited in numbers, and even they cannot fulfil the demand. In this regard, pharmacotherapy is a common practice compared to other therapeutic interventions. Most individuals prefer medication, and this trend is a little bit more popular, and a similar issue was faced in this study. This was one of the study's limitations in educating and motivating the patients to engage in treatment. Another issue was patients' lack of awareness and insight regarding mental health problems. Those who have some orientation about psychiatric problems prefer medication, and limited patients avail of psychotherapy. The majority avoid psychotherapeutic interventions due to active participation and self-effort to change behaviour. That's why it was complicated to engage the patients in treatment. The termination rate was higher because patients commonly believe in medication and poorly understand the mechanism of the psychotherapies. In this study, we included

Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 3, Issue 9 (2025)

Online ISSN 3007-3197
Print ISSN 3007-3189
http://amresearchreview.com/index.php/Journal/about

the patients with mild severity in an outdoor facility, and the study does not explain the patients who have moderate to severe intensity. COVID-19 pandemic was another hurdle in the different aspects of the study. This study does not explain the other depressive disorders and their severity and about the inpatients.

THE IMPLICATION OF THE STUDY

This study provides a valuable and rationale background to mental health practitioners to treat and develop guidelines and protocol for patients with major depressive disorder with mild severity. This study will promote the trends of practice the pharmacotherapy, psychotherapy, and Islam-based interventions as evidence-based treatment interventions. This study will help us treat patients with MDD-m by practicing PTh, CBT, and IBIs as collaborative and separate modalities. In Pakistan, most people belong to the Muslim religion; therefore, religious practices effectively educate and guide the patients because they have a basic orientation about the faith and its role in daily life functioning. In this regard, Islam-based interventions can also work effectively, but the given interventions are targeted and purposeful.

ABBREVIATIONS

CBT: Cognitive Behaviour Therapy, IBIS: Islam-Based Interventions; PTh: Pharmacotherapy; MDD-m: Major Depressive Disorder-mild; RCT: Randomized Control Trial; APA: American Psychiatric Association; PHQ-9: Patients Health Questionnaire; ICP-SWS: ICP Subjective Well-being Scale; DSS: Digit-Span Subtest; SPM: Standard Progressive Matrices; RSES: Rosenberg Self-Esteem Scale; DMQ: Decision-Making Questionnaire; PAS=Positive Affect Scale; NAS=Negative Affect Scale; LSS=Life Satisfaction Scale; TD=Thoroughness Domain; CD=Control Domain; HD=Hesitancy Domain; SD=Social Resistance Domain; PD=Perfectionism Domain; ID=Idealism Domain; ID=Instinctiveness Domain;

CONSENT TO PUBLICATION

Not applicable

COMPETING INTERESTS

All the authors declared that they have no competing interests

AVAILABILITY OF DATA AND MATERIAL

All supporting data can be provided at a reasonable request from the corresponding

Online ISSN 3007-3197
Print ISSN 3007-3189

author.

FUNDING

This research does not receive any funding from public and commercial agency.

ACKNOWLEDGMENT

Different psychiatric hospitals allow us to work with patients in their limited resources in this study. We are thankful to the hospital authorities and related staff who accommodated us during the study trial. We are also grateful to the research participants who participated in the study voluntarily and completed all tasks with commitment and responsibility. We want to thank those who initially participated in the research but could not continue due to their issues.

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