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Published online 2023 May **Systematic Review**

Evidence-based Non-Drug Interventions in the Management of the Psychological Consequences of the Prevalence Covid-19: A Systematic Review

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Abstract

Background: Patients of Covid-19 are susceptible to suffering of psychological disorders such as anxiety, worry, fear, hopelessness, confusion, insomnia and depression.

Objectives: The present study aimed to reviewing Evidence-based non-drug interventions in the management of the psychological consequences of the prevalence covid 19.

Methods: The present systematic review article was conducted by searching and screening related studies on databases of Scopus, Cochrane, Library, Web of Science, PubMed, Embase, in accordance with the PICO scale and PRISMA guidelines during the prevalence covid 19.

Results: Of the eight selected papers, two were in children and six in adults. In patients with a definitive diagnosis of COVID-19, a significant effect of internet-based integrated intervention was shown to reduce depression and anxiety (P<0.001). Online psychoeducational interventions resulted in a significant difference in increasing resilience (P=0.04) and reducing perceived stress of patients (P=0.01). Jacobson's relaxation technique intervention in COVID-19 patients indicated statistically significant difference in improving quality of sleep and decreases anxiety (P<0.001). The results of respiratory rehabilitation interventions and stretching exercises in COVID-19 patients were associated with improved pulmonary function tests, a significant increase in quality of life scores, and a significant decrease in depression and anxiety scores. Digital cognitive behavioral therapy significantly reduced depression and stress (P<0.001).

Conclusion: Psychological intervention can decrease depression and anxiety in healthy and patients of COVID-19 during a disease outbreak. Therefore, different psychological approaches can be effective in reducing anxiety during this stressful period.

Keywords: COVID-19, Evidence-based Practice, Non-drug interventions, Psychological Distress, Systematic review

1. Background

Infectious respiratory distress syndrome caused by COVID-19 was spread quickly from China to different parts of the world, and the World Health Organization was declared a public health emergency on January 30, 2020 (1). The latest global statistics on the prevalence of COVID-19 show that 76 countries are involved, with 88,340 COVID-19-positive cases recorded in these countries, of which 3,001 died and 42,728 improved (2).

In this context, the rapid human-to-human transmission of the virus has caused severe panic and stress among patients and healthy individuals (3, 4). The disease has caused panic and public concern. Having the disease raises anxiety and fear among people. Misinformation, rumors, misinterpretations, misunderstandings and ignorance of the disease increase the severity of anxiety. On the other hand, travel bans and some instructions, and house quarantine increase frustration and fear in the general population (5). Anxiety due to COVID-19 is common, which can be attributed to the unknown and ambiguous features of the disease; fear of the unknown feature reduces the perception of safety in humans. It has always been anxious for human beings (6). Depression and anxiety as a form of mental stress cause a series of physiological occurrence that lead to a decrease on immunity (7) . Also, plenty studies have shown that medical staff and patients of COVID-19 are more prone to psychological disorders toward the public population, including feelings of anxiety, worry, fear, hopelessness, confusion, insomnia, and depression, which can lead to severe psychological crisis if left unchecked. Therefore, mental health interventions and prevention of long-term psychological consequences of COVID-19 are important (8, 9).

The high prevalence of COVID-19 infection with the rapid increase numeral of patients and the great mortality rate has led to the limitation of providing medical services with a view to treating the disease in the short term; COVID-19 patients, on the other hand, suffer from psychological crises of varying degrees and at different ages (10). Patients' inability to tolerate situations and problems such as anxiety disorders, insomnia, fear, panic, restlessness, frustration, aggressive behaviors and blind optimism is easily understood in this crisis (11) and equally, the existence of effective and timely psychological interventions with important role at protecting the physical and mental health of patients has been

considered (1). After all natural disasters, the importance of rehabilitation has become apparent; SARS and MERS epidemics have been associated with similar experiences of mental health disorders (12). The results of studies on the recent COVID-19 pandemic have shown the highest prevalence of sleep disorders, anxiety and depression on patients (13). Dai et al. stated that the prevalence of anxiety and depression among patients of COVID-19 was 18.6 and 13.4%, respectively (14), possibly due to a lack of coping strategies, isolation, and reduced access to family, friend and social support systems, worsening patient tolerance and perceived stress (15, 16). The treatment cost, in addition to other causes, has greatly reduced patients' tolerance for the stress of illness (17). Therefore, any intervention that can help patients successfully reconcile and feel positive in the face of the recent stressful conditions of the recent crisis should be considered as primary care techniques, because reducing the adverse psychological consequences of COVID-19, especially in hospitalized patients, will increase patient's tolerance and satisfaction and increase the effectiveness of treatment (18, 19).

In a systematic review and meta-analysis of neurological and psychological consequences associated with the severity of COVID-19 disease, Rogers et al. found similarities between the mental disorders perceived by SARS-CoV-2 patients and the mental disorders of patients with SARS-CoV and MERS-CoV infections. According to the results of this study, most patients in the acute phase of disease experienced delirium and the post-disease period showed evidence of anxiety, depression and post-traumatic stress disorder. It is evident the importance of pandemic consequences, the need for patient follow-up and effective psychological interventions (20). Despite the recent COVID-19 pandemic, the survived patients are expected to suffer the long-term consequences of mental disorders. Therefore, the importance of supportive care and further studies in this field seems necessary.

Also Qi et al the prevalence of illness and psychological fatigue and its associated risk factors to patients of COVID-19 analyzed and understood that 43.9% of patients have mental health disorders, 12.2% of patient's have symptoms of post-traumatic stress disorder, 26.8 % of patients have anxiety and/or symptoms of depression and 53.6% of patients have symptoms of fatigue (21).

In total, drug therapy have potential side effects, consist of cognitive impairment and the risk of dependence or tolerance (22,23).There is no dependence or tolerance related with drugs for non-pharmacological interventions. Thus, non-drug interventions are used for patients based on their clinical needs mostly. Since there is not enough evidence of reviewing of non-drug interventions on psychological consequences, it seems necessary to conduct this study.

2. Objectives

In this regard, the present study aimed to systematically reviewing Evidence-based non-drug interventions in the management of the psychological consequences of the prevalence covid 19.

3. Methods

The present systematic review was performed by screening related studies published on databases including PubMed, Scopus, Web Of Science, Cochrane Library, Embase using keywords including COVID-19 OR (SARS-CoV, MERS coronavirus) AND (Mental Disorder OR Mental Illness OR Psychiatric Illness OR Psychiatric Disorders, OR Behavior Disorders OR Psychological OR Psychological Intervention OR Psychosocial Interventions, OR Psychiatric Rehabilitation OR Mental Health, Mental Health Services, OR, Cognitive Behavioral Therapies OR Psychiatric Somatic Therapies). The keywords were also searched individually and in combination.

The reference section of the review study and presented articles on the topic of article were also reviewed carefully to complete the research. The research results were merged in five databases, and the duplicates (Cases where the name of the author, year of publication and title of the study were the same) were excluded.

Two authors separately investigated title and abstract of papers, and the full-text articles were extracted and reviewed when they realized that topic is relevant to the purpose.

Inclusion criteria

The inclusion criteria were human studies with clinical trial design exploiting psychological (non-pharmacological) interventions in English and with access to the original articles. Also, the studies that were conducted during the prevalence of Covid-19 and only on patients by the diagnosis of Covid-19 were included in the study. Studies that were conducted as a non-drug intervention either alone or together with another treatments, and the intervention types include caregiver and patient behavior modification, hospital-based environment control actions, and home environment modification, and with approved RCTs, were included in the study.

Exclusion criteria

Case report studies, letters to the editor, non-human studies, and studies not directly related to COVID-19 infection were excluded from this systematic review. Due to the purpose of the study and in order to ensure the correctness of the elected articles, review articles, abstracts of conference papers, case reports, letters, editor notes and animal

studies were excluded. This cases where several publication from one research appeared to have been disseminated, only one with more complete data was included and another's omitted. This cases were identified by using the similarity of the authors' team, the similarity of the center and the time period of the study, and the similarity of the statistical results. This cases were recognized by using the similarity of the location and the time period of the research, authors' team, and statistical results.

Selection of relevant studies

The choice of relevant articles by two independent person in two steps was performed. In the phase of screening, the titles are first read and a decision is made to enter the analysis. The case of uncertainty in entering the articles, the abstracts were checked; titles and abstracts of articles must meet the exclusion and inclusion criteria. The cases that were doubtful and necessary to read their full text to make a decision entered the second step. This second step, the articles full text was reviewed and the articles that fully met the exclusion and inclusion criteria were included in a systematic review. In addition, all submitted articles, references of article and review articles were carefully reviewed on the topic to complete the search.

The final list of articles was checked by another researcher. The present review study was conducted following the PICO scale and PRISMA guidelines. The PRISMA 2009 flowchart (24) was used to report the selection and screening process (Figure 1).

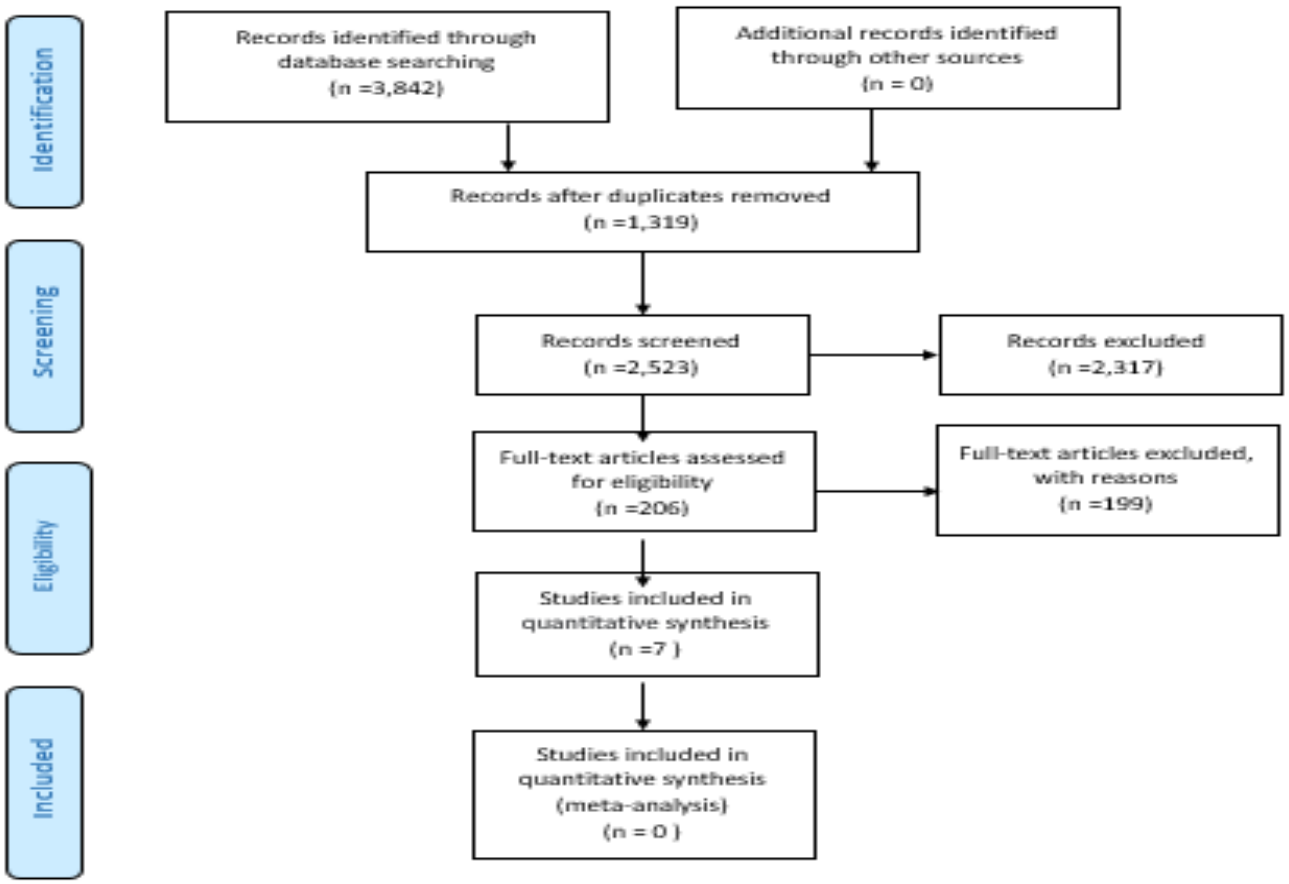

Figure 1. PRISMA statement (2009)

Data Extraction

The data extraction table was designed by the research team, and every articles in this study was checked via two researchers. The following information were extracted and presented in the table: name of first author, year of publication, region of study (country and city), sample size in intervention and control groups, age, study design, measurement instruments and main outcomes.

The quality assessment of included articles

Final Jadad scale consisting of three items was usage in order to assess the quality of included articles (25), which reports the fate of all patients in randomization (whether randomization was

performed and performed correctly) and blinding (whether the test was blinded and performed correctly), and method of randomization. Jadad scale was used to evaluate the quality of included articles (Table 1).

Table 1. Jadad Scale for reporting included randomized controlled trial

		Randomization			Blinding		Dropouts/Withdrawals			
	Non- Random allocation Point (0)	point if randomization is mentioned Point (1)	Randomized Point (2)	Non - Blinding Point (0)	Point if blinding is mentioned Point (1)	Blinded Point (2)	Non-mentioned Point (0)	Mention the numbers Point (0.5)	Mention the dropouts Point (0.5)	Jadad Score
1	Wei et al., (2020) [ref]		2	0			0			2
2	Shaygan., (2021) [ref]		2			2		0.5	0.5	5
3	Liu., (2020) [ref]		2	0			0			2
4	Liu., (2020) [ref]		2	0				0.5	0.5	3
5	Cheng., (2020) [ref]		2	0					0.5	2.5
6	Tang., (2020) [ref]		2	0				0.5	0.5	3

4. Results

The basic characteristics of the six articles reviewed in the present study, which were about the effectiveness of non-drug interventions on the psychological consequences of Covid-19, are summarized in Table (Table 2). A clinical trial study by Wei et al., (2020) in patients admitted to isolation ward with definitive diagnosis of Covid 19 using an integrated Internet-based intervention including four components: breathing exercises, mindfulness, shelter skills, and embrace Butterfly was applied every day for 50 minutes and for two weeks (during the study period). Due to the similarity of the two groups via of sex, age, disease severity and equal scores of the two Hamilton Depression and Anxiety Scales, after application Intervention and statistical analysis indicated a significant reduction (P<0.001) in the Hamilton Depression Scale and the Hamilton Anxiety Scale (26). Another clinical trial study by Shaygan et al., (2021) in eligible patients, admitted to 4 departments of 2 hospitals with a definitive diagnosis of Covid 19, used online psychological training interventions for two weeks. The basis of these interventions included cognitive-behavioral techniques, mindfulness, stress management and reduction, and positive psychology. After the intervention and evaluation of patients, a statistically significant difference was reported in increasing resilience (P=0.04) and reducing perceived stress in patients (P=0.01) (27).

Another clinical trial by Liu et al., (2020) in eligible patients with definitive diagnosis of Covid 19 Jacobson's relaxation technique interventions including progressive relaxation muscle exercises and deep breathing for 20-30 minutes daily for 5 consecutive days. Prior to the intervention, patients in the two groups underwent intervention and control of this Spielberger State Trait Anxiety Scale and Sleep State Self-Rating Scale, which were not statistically significant. After analyzing the study data, a significant reduction in the level of anxiety (P<0.001) and an improvement in sleep quality (P<0.001) were shown in the patients of the intervention group (28). Another study by Kai Liu et al., (2020) performed a ten-minute daily respiratory rehabilitation intervention with two training sessions per week for 6 weeks in patients admitted with Covid 19. Cough training, respiratory muscle training, diaphragm training and stretching exercises were performed in intervention group. Despite the absence of significant differences between the two groups before the study, the results of improving lung function, significantly increasing the life's quality questionnaire score and significantly reducing Anxiety and depression scores based on self-rating anxiety scale and self-rating depression scale showed after the intervention (29).

Another clinical trial by Cheng et al., (2021) among participants from previous studies between 2016 and 2017 who had insomnia based on the DSM-5 criteria during the Covid 19 crisis and its intervention a type of digital cognitive behavioral therapy, including six self-study sessions by cartoon virtual therapists. The results of this study reported a significant decrease in stress and depression (P<0.001) and an improvement in general health quality in the intervention group. Also, increased resilience of patients during crisis or in case of Covid 19 was shown in the intervention group contrast to control group (30). Another clinical trial study was performed by Tang et al., (2021) in patients via mild, moderate and severe degrees of Covid 19 and eligible

for the study. Patients in the intervention group received Liuzijue once a day for 20 minutes for 4 weeks of exercise, and after the intervention of functional exercise tests, a 6-minute walk, the British Medical Research Council (mMRC) scale, quality of life assessment And two scales were used to measure the level of anxiety and the level of Hamilton depression from the two groups of control and intervention. Based on results of this study, relief of difficult breathing, improvement of walking training capacity in 6 minutes, improvement of physical tests and significant increase in life's quality scores were reported. Also, the scores of the two Hamilton psychological scales decreased significantly (P<0.001) in the intervention group (31).

Table 2. Baseline characteristics of included studies (Description of intervention)

	Domain	First Author/publication date/country	Study design / Period of study	Population study/ Sample size/	Mean age in Year/sex	Inclusion Criteria	Type of interventions/ frequency	Measurement tool	Results/ outcome
1	**Psychiatric Illness**	Wei., (2020) ref China	prospective randomized controlled trial, *February. 2 to Feb. 28, 2020*	26 patients confirmed COVID-19 Intervention group (13) Control (13)	40-48 yrs. Intervention., (9 male/4 female), Control (7 male/8 female)	aged 18–65 yr. PHQ-9 or GAD-7 of ≥5; at least junior education	internet-based integrated intervention (breath relaxation training,mindfulness (refuge skills, and butterfly hug method./ Everyday (50 min) for 2 weeks	Hamilton Depression Scale; Hamilton Anxiety Scale	age, gender, severity of illness, (NS) reduced scores of 17-HAMD and HAMA (P<0.001), (Significant)
2	**Mental Health Services**	Shaygan., (2021) ref Iran	cluster randomized parallel-controlled trial April 2020	50 hospitalized patients (COVID-19), Intervention group (26), Control (22), 2 patients excluded	36.7 yrs Intervention., (13 male/13 female), Control (14 male/8 female)	age over 18 yrs., Confirmed COVID-19 hospitalized past 48 h, having internet and media access	online multimedia psychoeducational interventions: cognitive behavioural techniques, stress management techniques, mindfulnessbased stress reduction and positive psychotherapy (60 min) for 2 weeks	Sociodemographic Form, Connor-Davidson resilience scale (CD-RISC), Perceived Stress Scale (PSS)	Promote resilience (high level of adherence (80.76%) and Satisfaction (Mean = 29.42; SD = 4.18), Fewer perceived stress (p = 0.01), (Significant)
3	**Psychiatric Disorders**	Liu., (2020) ref China	Randomized controlled clinical trial 1 January to 16 February 2020	51patients confirmed COVID-19, Intervention group (25), Control (26),	50.4±13.04 yrs. Intervention., (14 male/11 female), Control (14 male/12 female)	Hospitalized with Confirmed COVID-19, Without any trauma and considering the strong infectivity of the new coronavirus	Jacobson's relaxation techniques (progressive muscle relaxation and deep breathing), Everyday (20–30 min) for 5 consecutive days Simultanusely takes a deep breath,	Spielberger State-Trait Anxiety Scale (STAI) and, Sleep State Self-Rating Scale (SRSS)	Reduced anxiety score , (P < 0.001) Improved sleep quality, (P < 0.001) (Significant)
	Domain	First Author/publication date/country	Study design / Period of study	Population study/ Sample size/	Mean age in Year/sex	Inclusion Criteria	Type of interventions/ frequency	Measurement tool	Results/ outcome
4	**Psychiatric Rehabilitation**	Liu., (2020) ref China	open Randomized controlled trial 1 January to 6 February 2020	72 patients confirmed COVID-19, Intervention group (36), Control (36),	50.4±13.04 yrs. Intervention., (24 male/12 female), Control (25 male/13 female)	age over 65 yrs., 6 months ≥ after the onset of other acute diseases; mini-mental state examination (MMSE) score > 21; No COPD or any other respiratory disease; and forced expiratory volume in 1 s (FEV1) ≥ 70%.	Respiratory rehabilitation (2 sessions per week for 6 weeks), once a day for 10 min.	pulmonary function tests, functional tests (6-min walk distance test), Quality of life (QoL) assessments (SF-36 scores), activities of daily living (Functional Independence Measure, FIM scores), and mental status tests (SAS anxiety and SDS depression scores)	FEV1(L), FVC(L), FEV1/FVC%, DLCO% and 6-min walk test (Significant) Decreased SAS and SDS scores after the intervention, but only anxiety had significant statistical significance within and between the two groups (P <0.05)
5	**Psychiatric Illness**	Cheng., (2020) ref China	Randomized controlled trial April 2020	208 patients Intervention group (102), Control (106),	44-46 yrs. Intervention., (28 % male 72.5%female),Control (16% male/	Individuals with a history of insomnia disorder higher risk of experiencing stress and	Digital cognitive behavioral therapy	22-item Impact of Events Scale (IES COVID-19)	increased health resilience larger impact on their sleep (p = 0.009)

					84%female)	insomnia symptoms during the COVID-19 pandemic,			
6	**Psychiatric Rehabilitation** **Catherine Malboeuf-Hurtubise1** **Catherine Malboeuf-Hurtubise**	Tang., (2020) [ref] China	Multicenter prospective self-controlled	33 patients confirmed COVID-19	33 eligible patients 43.2±10.4 yrs., With mild or moderate or severe cases	age over 18 yrs., Patients diagnosed with COVID-19, and meets the discharge criterion	Liuzijue exercise once per day for 20 minutes over 4weeks	Quality of life Short Form (SF36), Hamilton Depression Scale; Hamilton Anxiety Scale 6-Minute Walk Test (exercise capacity) modified British Medical Research Council (mMRC) scale (Dyspnea)	Increased significantly scores SF36-RP Reduced significantly scores (HAMD and HAMA) Improvment in Respiratory function and exercise capacity, Relieve dyspnea in patients (P=.022)

5. Discussion

The outbreak of the Covid-19 illness in all countries of the world has endangered the physical and mental health of people in the society, and due to its rapidly spreading, mysterious, unpredictable and uncontrollable has provided the basis for the spread of problem mental. The disease is created by a viral strain dependent to the coronavirus family (32). As the disease spread rapidly from China to another countries, the World Health Organization recognized COVID-19 on January 30, 2020 as a Public Health Emergency Concern (PHEIC). With an extra increase in the numeral of cases, the numeral of deaths and the numeral of countries affected globally, WHO declared COVID-19 as a pandemic on 11 March 2020 (33). This disease has a special complexity and has multiple dimensions and consequences that you can play a significant role in creating significant health, social and economic costs for individuals, communities and health services. The appearance of these illness is currently a public health crisis that brings with many challenges. There is a significant scientific slot in these field that definitions and information about it should be updated and reflected at all times (1). This disease causes a lot of anxiety and leading to changes and decreased quality of life (2). In addition, one of the certain data as to these illness is human-to-human transmission and its very much prevalence, which itself brings certain psychological and social risks. Currently, this disease has become widespread in Iran and has caused confusion and changes in living conditions. Patients with this illness should be treatment separately. Based on clinical observations, a lots of patients developed isolation, anxiety, and sleep disturbances after treatment. Anxiety, as a type of mental stress, causes a chains of physiological events and decreased immunity (7). Psychological disorders weaken the patient's immunity and decrease enthusiasm for treatment; Both of them have negative effects on disease rehabilitation (28). In this regard, in the study of Bo et al. (2020), it was found that the level of post-traumatic stress disorder in patients admitted with COVID-19 infection is very high (96.2%) (34), which is much higher compere that found in the people general (7%) (35). It has also been found that the risk of depression is higher among COVID-19 patients is too much (36). Infections have generally been found to be related with a higher risk of the mood disturbances (37), and appear to be at greater risk after intensive infections (38). This is consistent with findings from the SARS-CoV-1 epidemic, which showed depression symptoms in the duration of infection between patients (39). This higher hazard may be due to direct effect of the coronavirus on the brain straightly or indirectly through inducing a widespread cytokine response in the brain (40).

In the context of the COVID-19 pandemic, there appears to be a significant increase in depression and anxiety, substance abuse, domestic violence and loneliness. This concern is so considerable that the UK has exported a psychological first aid guide from the UK Mental Health Organization (41). This means that treatment protocols for COVID-19 patients should address both psychological and physiological needs of patients. Providing treatment and psychological support may reduce the burden of mental illness at the same time and ensure the health

of the injured. Providing psychological interventions in the field of mental health is likely to help patients keep psychological health and be more attuned to acute health conditions (42).

The COVID-19 pandemic, which has now outbreak to 213 countries and affected more than 13 million population, is expected to be followed by a massive wave survivors of COVID-19. They suffer from psychological disorders. These consequences acknowledge the importance of immediate efforts to prevent and directly intervene in patients' mental health. In the meantime, non-pharmacological therapeutic interventions promise efficiency without worrying about the side effects of drugs (43) and can increase conversation exchange, increase experience sharing, improve patients' adaptation to individual and collective life and increase the skills needed to deal with situations and relationships. There is currently limited knowledge about non-pharmacological interventions in the management of the psychological consequences of COVID-19 among inpatients and outpatients. In addition, the lack of evidence-based psychological interventions for patients with COVID-19 is quite noticeable. Therefore, this review study conducted with the aim of identifying non-pharmacological interventions on the psychological consequences of COVID-19 and also with the aim of providing documentary and scientific evidence about their effects. The results of meta-analysis demonstrated that non-drug interventions can recovered the COVID-19 psychological consequences. The findings of these systematic review were consistent by the formerly published systematic review of the efficacy of non-drug interventions on decreasing depression and anxiety in chronic obstructive pulmonary disease (COPD) patients (44).

The results of whole of six articles included in the present study showed a significant effect of based on Internet integrated intervention on reducing Hamilton Anxiety and Depression Scale (P<0.001) in patients with definitive diagnosis of COVID-19. Clinical trial with online psychological educational intervention reported a statistically significant difference in increasing resilience (P=0.04) and reducing perceived stress in patients (P=0.01). The current popularity of smartphones and Internet has much increased the efficiency of psychological health services in the epidemic of COVID-19. In the study of Rajab Dizavandi et al., (2021) it is mentioned that in order to prevent mental complications of covid-19 and improve the condition of these patients, psychological support in the form of telenursing intervention is needed (45).

The intervention of Jacobson's relaxation technique in COVID-19 positive patients demonstrated a statistically significant difference in reducing anxiety and improving sleep quality (P<0.001). The results of respiratory rehabilitation interventions and stretching exercises in patients of COVID-19 were associated with the results of improved lung function tests, a significant increase in quality of life scores and a significant decrease in depression and anxiety scores. Another intervention of digital cognitive behavioral therapy showed a reduction in stress and depression at a significant level (P<0.001) and improved general health quality and increased patient tolerance. The results of the Liuzijue exercise intervention showed an improvement in physical tests, a significant increase in quality of life scores, and a significant decrease in the scores of the two Hamilton psychological scales (P<0.001) in COVID-19 patients.

Study Limitations

Most of the counseling studies are in groups, while in individual education, it is easier to follow the participants and identify and control the confounding factors. Also, none of the studies included the number of participants in the intervention or excessive absences of participants in counseling sessions, since due to the spread of coronavirus, most virtual counseling courses were held. It can reduce the quality of work. One study showed that in comparison with virtual education with face-to-face education, the five principles of education programs were less observed (46). Also web-based survey (WBS) is associated with unexpected and total technical problems (47). However, most studies find technical problems in the study.

Strength of the study

The results of the present study can be decisive in future planning to improve the mental health duration the prevalence COVID-19. Also non-drug interventions in the management of the psychological consequences were identified, categorized, prioritized, and analyzed.

6. Conclusion

Psychological intervention can reduce depression and anxiety reported in patients with positive COVID-19 infection. Therefore, different psychological approaches can be effective in reducing anxiety in this stressful period. Although, the findings of the systematic review should be interpreted by caution because of the limitations. Also it is necessary to design scientific and more feasible randomized controlled trials to prove the efficacy of non-drug interventions on the psychological consequences of COVID-19 patients.

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from the Mashhad University of Medical Sciences.

Conflicts of interest

The authors declare that they have no conflict of interest regarding the present study.

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