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NON-SYSTEMATIC REVIEW

Psychiatry

Depresssion, anxiety and other cognitive consequences of social isolation: Drug and non-drug treatments

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Abstract

Objective: During the COVID-19 pandemic, quarantine and staying at home is advised. The social relationship between people has become deficient, and human social isolation (SI) has become the consequence of this situation. It was shown that SI has made changes in hippocampal neuroplasticity, which will lead to poor cognitive function and behavioural abnormalities. There is a connection between SI, learning, and memory impairments. In addition, anxiety-like behaviour and increased aggressive mood in long-term isolation have been revealed during the COVID-19 outbreak.

Methods: Term searches was done in Google Scholar, Scopus, ScienceDirect, Web of Science and PubMed databases as well as hand searching in key resource journals from 1979 to 2020.

Results: Studies have shown that some drug administrations may positively affect or even prevent social isolation consequences in animal models. These drug treatments have included opioid drugs, anti-depressants, Antioxidants, and herbal medications. In addition to drug interventions, there are non-drug treatments that include an enriched environment, regular exercise, and music.

Conclusion: This manuscript aims to review improved cognitive impairments induced by SI during COVID-19.

1 | INTRODUCTION

Social interaction has a crucial role in human well-being, both mentally and physically.[1] Human social isolation (SI) happens when the social relationship between individuals become deficient.[2] Moreover, it mostly occurs when the number of individuals, who are members of social links, decrease, or the qualification of social relations, diminishes. During SI, people experience unpleasant situations mentally, emotionally, and spiritually.[3,4] Some conditions force individuals to leave human groups and reduce their socia9l interactions, presence in the population, and group activities. Being single, getting a divorce and separation may also result in isolation.[2,5] Further, weak connections and lack of social support have shown to be significant risk factors of isolation, which result in loneliness, stress, and committing suicide.[6,7] Meanwhile, some infectious diseases such as COVID-19, AIDS and some physical disorders have shown to develop SI in humans.[8,9] Also, some studies have confirmed impairment in sensory processing is significantly correlated with depression. Extreme sensory processing patterns make humans feel hopeless and depressed.[10,11] As previous scientific research has described the association between vision disabilities and hearing problems with isolation and reduced human relation.[12]

Loneliness is considered as a risk factor for many psychiatric disorders such as adjustment disorder, chronic stress, insomnia and also late-life dementia[9] which may be long lasting.[13] Adverse effects on cognition and behaviour, decision-making, and pain perception are followed by social isolation.[14,15] SI has shown to change the immune system, glutamate system, and hormones.[15-17] Besides, cardiovascular disease, high blood pressure, stroke, and developmental neurodegenerative diseases have occurred during SI.[15] It has been

demonstrated that even short periods of SI are associated with increased psychological distress such as panic and emotional disturbances[18] and a study of Canadian people reported that these effects were greater among females.[18] Depression, lowered self-esteem, alienation and helplessness[13] was also induced while motor dysfunction decreased during isolation.[16,17,19] In the case of COVID-19 pandemic, the effects are exacerbated by prolonged SI, fear of the infection, frustration, boredom, inadequate supplies and information, financial loss, and stigma.[20]

Some evidence demonstrated more oxidative stress and inflammation because of increased IL-1β, cytokines, and brain macrophages during SI.[21] Isolation and loneliness lead to a higher rate of morbidity, mortality and it is strongly related to chronic disease with death in adults.[17,21]

Previous researches have shown there is a relation between SI and alternations in the hippocampus. According to studies, changes in hippocampal neuroplasticity will lead to poor cognitive function and behavioural abnormalities.[22,23] There is a connection between SI, learning, and memory impairments as well. Some studies have reported that environmental factors play a significant role in brain development and cognitive function in rodents, which directly affect learning and memory performance.[24,25] Results suggest that SI as the lack of presence of others or the few numbers of meaningful relationships is vastly associated with many aspects of memory and learning impairment.[26,27] Morris Water Maze's outcomes have also shown spatial learning and memory dysfunction during isolation.[28,29] Other studies have demonstrated inhibition of autophagy by the production of some factors,[29] deficit spatial learning and memory, social recognition memory, reversal learning, and short-term memory during SI periods.[30] Alternatively, some studies have shown that isolated environments did not affect spatial learning and memory, spatial reference memory, reversal learning, and short-term memory. Moreover, in some cases, results have suggested that memory and learning performance has improved because of social isolation.[31]

Animal research indicated depression, anxiety-like behaviour, and increased aggressive mood in long-term isolation.[32,33] Moreover, the time spent in the open arms of the Elevated plus Maze has decreased as a consequence of higher anxiety.[34]

Prolonged SI is associated with an increase in mortality of almost a third.[20] People with serious underlying physical and mental health conditions [35] and those who are socioeconomically disadvantaged are at higher risk.[36]

Regarding sleep quality in the face of SI during COVID-19, a study reported that 44% of respondents stated that they were sleeping the same number of hours they did before SI. However, 56% reported some change in sleep hours, breaking down into those who are sleeping more hours than usual (26%) and people sleeping less hours than usual (31%). Regarding physical activity, 40% of people are doing some exercise, and 60% are not.[37]

A study evaluating psychological repercussions of objective isolation in 1,006 Italians during the COVID-19 pandemic showed that the longer the isolation and the less adequate the physical space where people were isolated, the worse the mental health (eg, depression).[38]

According to studies currently done anxiety and chronic stress, in addition to depression and frustration are caused by the COVID-19 outbreak. In other words, in vulnerable ones, the pandemic condition has coincided with high-stress levels and disappointed feelings. According to a clinical study on china population, 16.5% of cases stated moderate to severe depression status, and 28.8% stated moderate to severe manifestation related to anxiety. because of stress and depression mood, sleep standards were changed, and the suicide rate has increased.[39,40]

A unique global online survey of 13 660 participants from 62 countries by using mixed-effects models showed that SI significantly predicts poor mental health operationalised as COVID-19-induced distress. At the aggregate level, average distress varies positively across countries with higher numbers of coronavirus-related deaths and more fragile state capacity, while varying negatively across those with more stringent anticoronavirus policies.[41]

Recent clinical investigation exhibited the percentage of psychiatric traits among 402 patients who got infected by COVID-19 and survived. At the end, results illustrated 20% for OCD (Obsessive Compulsive Disorder), 30% on average for depression, and as the

Take-home messages

Cognitive changes induced by SI during COVID-19 can be ameliorated by drug and non-drug treatments. In this review, only the treatments that ameliorate cognitive impairments induced by SI are introduced. There are no evidence that compare the effect of these treatments with each other. Further researches are needed to evaluate the effectiveness of each treatment and compare them in the future.

Methodological aspects

The database used to gather articles included; Science Direct, PubMed, Scopus, Web of Science and Google Scholar. Firstly, authors collected 100 articles using keywords relevant to COVID, Corona, isolation, mental and cognition illness, then, investigators reviewed data and find more keywords searching in scientific source and valid journals, for example, depression, frustration, anxiety, aggression, neuroplasticity, social isolation, learning and memory. Secondly, every mentioned word was investigated in articles that included alternations were made thorough the isolation, therefore, we searched two types of drug and non-drug treatments to decrease the mentality disorders and cognitive changes. Finally, 200 articles were selected and irrelevant data removed, and we conducted 154 studies from 1979 to 2020 to review the main treatments used for alleviating isolation side effects.

same for PTSD (Post-traumatic stress disorder), and about 40% for anxiety and as the same for insomnia. Nevertheless, pathological and molecular evaluations explained how inflammatory factors bring about psychopathological signs owing to COVID-19 infection.[42]

Also, a public opinion poll and set of questions were attributed between Iranian people to survey the quantity of anxiety in the population throughout the COVID-19 pandemic. In consequence of more than 10 000 completed documents that were informed by persons from different provinces, statistical analysis has described clinical data. According to collected information, women who had regard to news published about the corona, and the daily number of dead, got more anxiety level, and individuals from 21 to 41 years old. However, people who had more friends and relationship has felt less anxiety and stress, but educated people experienced more anxious conditions.[43]

The human species depends on social behaviour and social interaction. Being social helps humans survive and solve problems; while, weak social interaction negatively affects social memory and sociability during SI.[33] There has been a correlation between neuroendocrine disability and impairments in neurogenesis of the hippocampus and decline in BDNF expression[44,45]

The results have also revealed that SI has developed Alzheimer's disease, and it has exacerbated spatial learning impairment in aged mice.[46] Motor activity is not affected according to open field outcomes; however, chronic stress during SI has shown to the deficit the motor function in rodent models of Parkinson's disease.[47,48]

2 | DRUG TREATMENTS

Studies have shown that some drug administrations may positively affect or even prevent social isolation consequences in animal models.

1. **Opioid drugs:** These are measured by pinning configuration and rats use them to defend nap access. According to the previous play investigation, fighting became greater in junior rats during short-term social deprivation. Social grooming, as a behavioural factor by young and adult animals, is performed in rodents and primates. Both behavioural responses among primates, particularly humans, accounted for increasing isolation because of neurochemicals and opioid systems involvements.[49-51]

Naltrexone treatment by subcutaneous injection in a dose range of 0.03-1 mg/kg body weight was administered. It has decreased pinning duration, frequency, and grooming behaviour dose-dependently.[50,52]

Apomorphine treatment by subcutaneous injection in 2 doses of 60 and 100 pg/kg has significantly reduced pinning duration and frequency in a dose-dependent manner. In addition, a 35 pg/kg dose of apomorphine decreased grooming behaviour.[50,53]

β-Endorphin treatment in a dose of 100 pg/kg has decreased the duration of pinning, but not for the time of grooming.

In conclusion, some opioid drugs have improved social activity by regulating the opioid receptors and neuronal systems.[50,54]

2. **Oxytocin:** Genetically, lower levels of oxytocin in some mice or hypersensitive receptors to some stressors caused mental illness and reduced social interaction.[55] On the other hand, stressful experiences and accidents may result in the overproduction of oxytocin in the central and peripheral nervous system. Long-term SI significantly led rodents to be immobile, less active and depressed. The social environment has regulated oxytocin production in specific regions in the CNS.[56,57]

In some rodents, administration of exogenous oxytocin for a long time has blocked weak social contact and behavioural impairments, such as depression during SI.[58] However, oxytocin can perform as an antidepressant drug and decrease negative social interactions as well as encourage isolated ones to get over it.[59] Other investigations have described how oxytocin developed stress response consequences of separation in female rodents.[60-62]

Stress is often accompanied by isolation-induced alternations on neurochemicals; subsequently, depression and anxiety disorder. Previous studies have revealed the injection of oxytocin with inter-central amygdala procedure in mice resulted in improvement in depression and anxiety behaviour.[63] Many investigations have explained, amygdala activity has been regulated by oxytocin. Oxytocin can also perform as an anti-anxiety and anti-depressant drug to treat isolation-induced social stress after 5-weeks of social isolation. Long-term SI has decreased OXTR mRNA transcription and GABA level in mice and induced anxiety-related behaviour and depression.[55,64] Oxytocin administration has attenuated depressive-like, anxiety-like and destructive social behaviours. Anxiety measurement was performed with an open field test (OFT) and the elevated zero maze test (EZMT) in mice[57,65]

3. **Antidepressant drugs:** According to previous investigations, decreased BDNF level and neuro-steroids in the hippocampus were induced by SI and depression in adults. Published data have shown antidepressant treatment such as **fluoxetine** and **fluvoxamine** increased BDNF mRNA expression.[66,67] Neurosteroids such as **allopregnanolone** reduced aggression and anxiety-like behaviours. The stable emotional mood in rodents has made them successful in improving social support and less isolation because of allopregnanolone performance on GABA neurotransmitters.[68,69]

It has been revealed that a selective serotonin (5-HT) reuptake inhibitor such as Fluoxetine is able to alleviate isolation-induced depression behaviour.[70] Oral Fluoxetine consumption has improved the depletion of serotonin in the hippocampus; and, anxiety, depression, and social deficits have reversed during social isolation. Moreover, brain neurogenesis has improved, which plays a crucial role in

emotional deficit development.[71-73] With Fluoxetine treatment, as an anti-depressant, metabolic impairment was also reversed.[74] Some documents have claimed that Fluoxetine that is attached to mitochondria can change anion channels voltage, and finally, alleviate depression.[75]

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRI) antidepressant, that has been widely used for MDD, anxiety and neuropathy.[76] Venlafaxine is also effective for patients with treatment-resistant depression.[77] This drug (5 mg/kg/day) is been shown to alleviate the loss of myelin and oligodendrocytes (OLs), mitigate depression-like behaviours, and improve cognitive function in cuprizone-fed animals.[76] Twelve weeks of treatment with venlafaxine (≤300 mg/day) does not exert meaningful changes in motor cortical inhibition or plasticity in late-life depression.[78] Venlafaxine improves social phobia and avoidant personality disorder symptomatology in SSRI non-responders.[79]

While SI could cause cognitive dysfunction and decrease synaptic protein (synaptophysin or PSD93) expression in different brain regions associated with cognition in middle-aged rats, the SSRI antidepressant **citalopram** (10 mg/kg, ip) could significantly improve learning and memory and partially restore synaptophysin or PSD93 expression in the prefrontal cortex, hippocampus, and amygdala in SI rats.[80] Administration of 10 mg/kg (ip) attenuates Tau hyperphosphorylation and spatial memory deficit induced by SI rearing in middle-aged rats. Citalopram could partly restore the level of melatonin levels in SI animals. It could increase MT1 and MT2 in mRNA level in the hippocampus. Melatonin negatively regulates GSK-3β and attenuates tau hyperphosphorylation and spatial memory deficit induced by SI in middle-aged rats.[81] Moreover, isolation housing increased somatodendritic (+52%) and postsynaptic (+30 to 95%) 5-HT1A as well as postsynaptic 5-HT2A receptor binding (+25 to 34%). Isolation-induced receptor binding changes were partly normalised by chronic citalopram treatment (3 weeks, 20 mg/kg, ip daily). Chronic citalopram-induced alterations were more pronounced and affected more brain regions in isolates than group rats, supporting the concept of higher responsiveness in "stressed" animals.[82]

Duloxetine is believed to potentiate serotonergic and noradrenergic activity in the CNS.[83] Duloxetine's mechanism of action involves the simultaneous inhibition of serotonin and norepinephrine uptake. It is also used for the management of pain associated with diabetic peripheral neuropathy.[84] Item-based analysis of data from placebo-controlled trials revealed that this drug exerts a robust reduction in depressed mood and other core symptoms of depression.[85] The recommended dosage of duloxetine is 40-60 rag/day for depression, 60 mg/day for neuropathic pain, and 80 mg/day for stress urinary incontinence.[84] Duloxetine dose-dependently decreased ethanol intake in animals that were isolated throughout adolescence.[86]

Escitalopram is recommended as first-line therapy for MDD and severe depression.[87] It is reported that escitalopram may have greater efficacy and a faster onset of action than citalopram[88] and other antidepressants[89] and also successful patient tolerance over a 12-month administration. Escitalopram, as a SSRIs, administration increases the level of 5-hydroxytryptamine in the serotonergic system, including prefrontal cortical area, amygdala, ACC and hippocampus.[87] In the study of non-depressed patients with recent stroke, escitalopram administration resulted in a significantly lower incidence of depression over 12 months of treatment.[88] Chronic treatment with escitalopram (5 or 10 mg/kg/day, ip) prevented the decrease in sucrose intake in approximately 50% of the treated rats and reversed the decrease in cytogenesis in the dentate gyrus of the ventral hippocampal formation in a chronic mild stress rat model of depression, but only in recovered animals from anhedonia, as measured by cessation of behavioural deficits.[89] It's been shown that even a single dose of escitalopram is sufficient to alter the brain's functional anatomy even in a short term. Moreover, Escitalopram (10-20 mg/day) was well tolerated and effective in patients with social anxiety disorder.[87,90]

Paroxetine as a selective serotonin-reuptake inhibitor that seems to be a good candidate because of the absence of active metabolites, and favourable side-effect profile, including lower levels of cardiotoxicity than those of tricyclic antidepressants. In patients with malignant melanoma, treatment with the antidepressant paroxetine (31 mg of paroxetine per day at the maximal dose) significantly attenuated interferon alfa-associated symptoms of depression, anxiety, and neurotoxicity and decreased the incidence of major depression during high-dose interferon alfa therapy. Paroxetine may enhance endogenous feedback pathways that regulate the production of cytokines such as tumour necrosis factor α, interleukin 1 and interleukin 6, which are potent inducers of sickness behaviour and neurotoxic effects in humans and animals.[91] Moreover, Paroxetine has been used as the antidepressant treatment for tumour-depressive mice.[92] It's been shown that paroxetine (10 mg/kg/day paroxetine for 28 days, ip) combined with chemotherapy drugs improved depressive behaviour and promoted the survival state in a mouse model of colorectal cancer and depression, possibly through improving immune status by inhibiting IL-22 expression to regulate the activity of the MAPK signalling pathway.[93] Paroxetine treatment (with dosage adjusted during 1-2 weeks to a target of 40 mg/day) normalised regional brain metabolic abnormalities at baseline, in some brain regions such as prefrontal cortex, anterior cingulate gyrus and temporal lobe in MDD patients.[94] Moreover, paroxetine (10-60 mg per day) reduces social anxiety in individuals with a co-occurring alcohol use disorder.[95]

Sertraline is a modern and relatively safe SSRI often used in the treatment of depression. It also has a weak affinity for α1-adrenergic receptors and to a small extent inhibits the dopamine transporter.[96] It seems that sertraline could attenuate PTSD symptoms since individuals who received sertraline (with the average dose of 115 mg/day) may feel more inclined to engage in pleasurable activities, decrease isolation, and increase social interactions as their PTSD symptoms are reduced.[97] Sertraline treatment (10 mg/kg/day, ip) for 7 days reduced the depression-like effect in rats reared in enriched condition and standard condition, but not in socially isolated rats. It decreased anxiety-like behaviour in socially isolated rats while

increased in enriched rats.[98] In addition, sertraline upregulates and increases BDNF levels and enhance neurogenesis in the rodent brains.[99] Moreover, it's been reported that chronic administration of sertraline increases the expression of cAMP response element binding protein (CREB) in the rat hippocampus.[100] Administration of fluoxetine; sertraline and tianeptine has been attenuated the cognitive deficits observed in isolation-induced depressive rats.[101] In socially isolated voles that treated with sertraline (16 mg/kg/day, ip) during isolation, sertraline did not protect against depression-relevant behaviours, and it was associated with increased short- and long-term heart rate responses. However, sertraline administration improved heart rate variability recovery following a behavioural stressor, including increased parasympathetic regulation and altered long-term neuronal activity in brain regions that modulate autonomic control and stress reactivity. Sertraline administration was associated with decreased central amygdala and increased hypothalamic paraventricular nucleus activity, which may consequently reduce excitatory input to the sympathetic nervous system and/or enhance tonic parasympathetic cardio-regulatory control.[102]

Clozapine has been known as an effective drug to improve the social deficit induced by SI. This research has shown alternation in corticostriatal ATP levels, anti-inflammatory cytokines, and neuroprotective ratio through isolation condition.[103] The whole alternations were reversed by Clozapine, as an atypical antipsychotic, to improve SI detriments and particularly depressive behaviours.[104] Anti-depressant properties of Clozapine have made it beneficial to prevent isolation-induced depression in rats.[105] Molecular investigations have shown Clozapine has decreased TNF-α, GPX, and glutamate-like receptor significantly; plus, less GLR activity of cyclooxygenase-2 (COX-2) and interleukin-1beta (IL-1β) in the hippocampus were induced by Clozapine.[106] Administration of Fluoxetine and Clozapine, as non-steroidal anti-inflammatory drugs for three weeks in rats, prevented quanta decline in hippocampal parvalbumin-positive (PV+) cells.[107]

Increased GSH content and nuclear factor-kappa B (NF-kB) has led to reduced depressive-like and anxiety-like behaviours in isolated rats[108]; while Leponex (25 mg of CLZ per tablet) was administrated for 21 days. More research has revealed low doses of Clozapine (0.1, 0.2, and 0.4 mg/kg) can exert anxiolytic properties in isolated rats and reduce anxiety behaviour, stress, and depressive mood.[104]

Besides, chronic administration of Fluoxetine is effective in treating SI-induced impairments of spatial learning and memory, cognition, neurogenesis, emotion-related, and depressive-like behaviours in rodents. Further, Clozapine has found to improve behavioural deficits and activate some regions in the brain, such as dHIPP and RSC, associated with memory, learning, and spatial orientation in socially isolated rats. Moreover, long-term administration (6-8 weeks) of Clozapine (5 or 10 mg/kg) has shown to improve the reversal learning deficit in SI rats.[34,109]

Another investigation revealed that 5 to 10 days of consumption of antipsychotic drugs, such as ampakine and aniracetam, have reversed the impairment of recognition memory in isolation-reared rats.[110-112] Further, administration of Methylphenidate (1-10 mg/kg) and Caffeine (0.5-1 mg/kg), which are commonly used for attention deficit hyperactivity disorder (ADHD), have shown to be efficient for latent learning and spatial attention impairment.[113] Moreover, a low dose of corticosterone increased the expression of the activity-regulated cytoskeletal associated protein (Arc) and improved long-term memory in socially isolated rats. Other studies have shown that inhibiting receptors via antagonist drugs might reverse SI impairment in rodents.[114-116]

Administration of **5-HT6 receptor antagonist drugs** can potentially bring back learning, cognition, and recognition memory deficit by up-regulating glutamate and serotonin in cortical and hippocampal regions in SI-reared rats.[117] Results suggested that **PRX-07034** and **PRX-07037**, as 5-HT6 antagonists, reverse the isolation rearing-induced memory deficit, while **Ro 04-6790** diminishes the effect of isolation on reversal learning impairment.[118] In addition, **Ro 4368554** has been able to reverse a scopolamine-induced impairment in emotional learning.[119]

SI has shown to elevate **Rac1 activity** in hippocampal tissue, inducing social recognition memory (SRM) forgetting and long-term potentiation (LTP) decline in mice; According to this finding, Inhibiting of Rac1 Activity Blocked Progressed Decline of LTP and suppressed forgetting of SRM in isolated adult mice. However, Rac1 activity had no influence on short-term (15-min) memory in the socially isolated period.[120]

Additionally, Results have revealed that in socially isolated mice, the excitatory presynaptic release of pyramidal neurons in the mPFC has attenuated, and metabotropic **glutamate receptor 2/3 (mGluR2/3) antagonist, LY341495**, played a crucial role in recovering working memory by building reasonably vast synaptic strength in the mPFC in SI-reared mice.[121] Further, a single treatment with **LY341495** improved isolated mice performance in the Y maze test but not in the novel object recognition test, while repeating the treatments were efficient for both tasks.[121-123] Conversely, mGluR2/3 agonist, **LY379268**, has also improved recognition memory impairment in SI rats.[121,124] Earlier investigations have suggested that stress and anxiety-like behaviours have appeared because of a mediator called the Corticotropin-releasing factor (CRF). CRF agonist injection has shown additional anxiety in the Elevated plus Maze and open field tests in rats. During isolation and social impairment, the CRF receptor has been increasingly activated in the DRN and this result in anxiety-like behaviours. Subsequently, researchers have administered **CRF receptor antagonists**, which decreased stress and anxiety.[125,126]

4. **Antioxidants**: Isolation-induced oxidation stress has led to many cognitive impairments, such as violence, aggression, and anxiety. Reactive Oxygen Species have been produced by oxidative stress and they caused variable damages to the brain structurally and physiologically.[127] Researchers have decided to evaluate the administration of antioxidants in isolated mice to reduce social and behaviour deficits such as aggression for 14 days. Eventually, results have revealed vitamin E in high doses and N-acetyl cysteine in low doses were effective to decline aggression in

isolated mice. A low dose of vitamin E and N-acetyl cysteine beta-carotene in high doses were effective in reducing acute isolation-induced aggressive behaviours. However, ascorbic acid has exhibited a more dose-dependent behaviour. Biochemistry procedures have evaluated antioxidant markers; while, molecular results have shown the level of catalase, superoxide dismutase enzymes, and glutathione. Data have suggested an increase in biomarkers among isolated mice treated with antioxidants. Researchers found that antioxidants consumption after 14 days has improved aggressive behaviour in isolated mice.[128,129]

5. **Herbal drugs:** Central nervous system disease had been treated in ancient Korea and China until now, by **Uwhangchungsimwon (UCW)** as a herbal drug. Researchers have kept mice in separate cages to induce isolation for 31 days. Isolated mice were shown to be depressed, while those mice, which had oral administration of UCW every day, after 17 days, have shown improvement in behavioural tests and significantly reduced depressive-like behaviours. Improvements were justified according to an increased level of serum corticosterone and a higher level of dopamine, serotonin, and norepinephrine in the hippocampus. This investigation has shown that UCW consumption has diminished isolation-induced depression in mice by ameliorating neurochemicals.[35]

3 | NON-DRUG TREATMENTS

1. **Environmental Enrichment (EE)**: It has been indicated alternations in neurotransmitters levels such as glutamate, serotonin, and decreased BDNF induced by chronic isolation were modified in EE.[123] Social activity among rats exposed to a novel environment was higher than standard rats. These results proved the potentiality of non-drug protocols in improving mental deficits.[130] Moreover, well-being in isolated patients is related to the quality of social support; consequently, any prescription to encourage being social and connected has been considered by the practitioner.[131] EE, as a non-pharmacological treatment, has been applied in some investigation. Data have suggested that EE has enhanced social and cognitive deficits in isolated patients. Several researchers have exhibited the importance of positive and hopeful experiences in life to recover the brain from behavioural dysfunction.[132]Anti-depressant effects of EE have been demonstrated by investigations according to SI in rats.[133] It has been shown that depression-related behaviour and related abnormalities followed by long-term isolation, could be treated by EE. It can also perform as effective as fluoxetine; however, side effects associated with a pharmacological drug would not happen with EE treatment. Isolation-induced decrease in 5-HT level has been regulated through EE treatment, and the 5-HT level has increased in the hippocampus and prefrontal cortex. Finally, some investigations revealed that using an EE increases the rate of neurogenesis to maintain the proliferation of dentate gyrus (DG) hippocampal cells in socially isolated mice, which results in maintaining social recognition memory and improving amnesic-like impairment.[134]

In conclusion, EE plays a significant role in promoting neurogenesis in the hippocampus, impaired by social isolation.

2. **Exercise:** Frequent physical exercise has been accepted among people to improve the physical and emotional conditions. By designing several studies on sports achievements, it has demonstrated that neurotransmitters' functionality and brain plasticity have been modulated in socially isolated rodents.[135] In several types of research, rats were forced to run on a **treadmill**, which was a stressful condition. Results were disparate compared with voluntarily exercise, which resulted in regulating BDNF levels in isolated rats. Some other investigations have revealed that elective exercise cannot make any improvements in cognitive and social behaviour impairments.[136,137] Eight weeks of running on a treadmill (30 min/day) have been shown to improve short-term and spatial working memory in SI rats.[138] Regular treadmill exercise has improved isolation-induced depression-like behaviour by regulating the hypothalamic-pituitary-adrenal (HPA) axis and this type of exercise has decreased stress hormones. Additionally, increased BDNF, NGF, serotonergic cells and brain plasticity in the hippocampus have occurred after physical activity.[139]

Clinical research has revealed that **walking** among adults has positively affected social experiences for people who have been isolated and lived alone. At the end of this research, adults have claimed an improvement in their feelings and are encouraged to start social relationships, to get to know new people, and finally, to leave isolating mood.[140,141] As stated by the research on rats, it has indicated that the development of monoaminergic axons has been prevented during isolation periods in maternal separation.[141] Eventually, **voluntarily running exercise** has been found to stop emotional and social impairments by stimulating monoaminergic axons to start improvements again.[142]

As claimed by more studies, pro-inflammatory and cytokine interleukin-1β (IL-1β) has been produced increasingly in the hippocampus during the adolescence period. Besides, Social isolation adversely affects the hippocampus neurogenesis. Adolescence is a critical period in hippocampus maturation, and any detrimental impact makes more impairment in adulthood.[143,144] These Researches have found that **aerobic exercises** decreased stress induced by both adolescence and isolation in the hippocampus. Eventually, it has been demonstrated by some evidence that overexpression of IL-1β has been reversed by running and aerobic exercise during isolation housing in adolescence; while supportive effects on neurogenesis occurred at the same time and resulted in developed recognition and social activity.[145] These findings explained how SI changed 5-hydroxytryptamine expression, and led to apoptosis in rats, which can account for cognition deficit and anxiety mood. Investigations have also designed an experiment to explore **swimming** effects on socially isolated old rats.[35]

Tryptophan hydroxylase positive cell, 5-hydroxytryptamine positive cells, and Bcl-2 (B-cell lymphoma 2) expression have increased

TABLE 1 Non-drug treatments

Non-drug treatment	Observed effect(s)
Enriched environment	Promotes social activity,[130] improves cognitive deficits[132] and attenuates depression-like behaviour[133]
Exercise	
Treadmill	Improves memory[138] and attenuates depression-like behaviour[139]
Walking	Improves social behaviour[140,141]
Running	Prevents emotional and social impairments[142] and reverses overexpression of IL-1β[145]
Aerobic exercise	Decreases stress in the hippocampus and reverses overexpression of IL-1β[145]
Endurance exercise	Attenuates adverse effects induced by SI[147,148]
Swimming	Prevents apoptosis, reduces anxiety, and enhances social and learning capability in rats[146]
Music	Reduces fear and stress, improves social relationships[152]
Technology	
Smartphones	Increase social interaction[154,155]
Social engagement	Improves age-related cognitive deficits, dementia, and memory decline induced by SI[156]
Social robots	Provide social support and reduce depressive-like mood[157-159]
Farming	Promotes social interaction[160,161]

while BAX (Bcl-2-associated X protein) and cytochrome c expression were suppressed while swimming exercise. It was shown that swimming would lead to apoptosis prevention, reduced anxiety, and enhancement in social and learning capability in rats.[146]

As claimed via an earlier investigation, depression was seen after periods of SI, which impaired the glutamatergic system in the hippocampus and NMDA receptor co-agonist D-serine. It has revealed that **endurance exercise** has attenuated adverse effects induced by isolation.[147,148] Amelioration of glutamate transmission has also decreased depressive behaviour in rats. Therefore, exercising has been able to decline depression, social deficits, and cognition impairment induced by isolation experiences.[149]

3. **Music:** Music is well known as a way to express emotion and has effects on well-being feeling, regulating hormones, and neurotransmitters. Physicians have found music therapy as a method to alleviate patients who had shown regression and weak sociability during housing isolation.[150] Two types of patients, adults in the general ward of the hospital and children with leukaemia in an isolated room, have experienced it as an enjoyable practice.[151] They have claimed reduced fears, stress, and a motivated mood by listening to music. Besides, more verbalisation, self-expression, and social relationships were reported. Beneficial impacts of listening to music have been performed by neurochemicals such as dopamine and oxytocin, which resulted in active talking and better communication. It has also enhanced health conditions in patients with Parkinson's disease by increasing social benefit. In conclusion, music has been considered a non-pharmacological treatment in isolated patients and SI.[152]
4. **Technology:** As mentioned earlier, the environment itself plays a critical role in brain function and development. Lack of social interaction, as an absence of social stimulation on the brain, may lead to lesser cognitive reserve, lower brain flexibility, and cognitive impairment.[153] There are several investigations on using **smartphones**, which have been used as a critical tool to connect humans and plays a crucial role in social capability and decreasing SI.[154] Nowadays, social interaction has strictly wired into mobile phones via social platforms such as chat rooms, groups and channels, YouTube videos, and video-call applications such as Skype. During the pandemic, when getting quarantine and staying at home was advised, social support has been provided mostly by social media throughout smartphones. People could join in social activities and feel like a helpful member of the community to reduce the detrimental effects of isolation.[155] **Social engagement** has shown to improve age-related cognitive deficits, dementia, and memory decline induced by SI. Moreover, a sense of belonging and connection with others in places such as school has shown to be crucial for academic success.[156]

During the COVID-19 pandemic, Attitudes towards **social robots** have changed. Pieces of evidence have shown that people were encouraged to buy social robots more than ever. The emotional and behavioural features of those robots have made people feel less lonely and isolated; also, social support and reduced depressive-like mood were reported. A sense of happiness and having a better quality of life was seen through interactions with a robot, which was designed to behave socially interactive.[157-159]

5. **Farming:** Farming activities have been shown to regulate social functioning for those who are suffering from a mental disorder. Several investigations have revealed that farming activities moderated getting into the community and having a connection with people. Being with each other is essential for people with mental problems; therefore, drug treatments will not work when social bonds are weak. According to the current research, social farming has been useful for social interaction and to fight against isolation.[160,161] Non-Drug treatments are shown in Table 1.

4 | CONCLUSION

This review presented an overview of available studies on social isolation, adverse effects on cognition and possible treatments. A wide range of studies has been collected and retrieved to explain beneficial treatment methods. Learning and memory impairments, anxiety and depressive-like behaviours and social deficit consequences of social isolation have improved by prescription of some opioid drugs, anti-depressants, antipsychotics, and a variety of antagonists. Moreover, antioxidants and herbal medications have found helpful to ameliorate isolation side effects. Besides, an enriched environment, regular exercise, and music, as non-drug treatments, have shown to be beneficial for isolated people. Finally, the application of technology and farming activities have suggested improving isolation-induced cognitive and social impairments.

5 | LIMITATIONS

We encountered several limitations to make a noticeable review, which should be considered. First, some publications were written in a non-English language, so we were not able to recognise the results. Second, several related articles were not available in free access and we could not utilise the information, therefore became replaced by others. Third, despite the fact, the most relevant keywords were used in searching, some papers were not directly correlated to this review, so they caused wasting time for researchers and make them tired. Despite some challenges, this review provided considerable outlines that improve impaired cognitive properties induced by SI during COVID-19.

DISCLOSURES

This study was supported by Kerman Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran. Since the review articles analyses or discusses research previously published by others, rather than reporting new experimental result, therefore, no consent has been used in this study.

AUTHORS' CONTRIBUTIONS

All authors were involved in the conception and writing of manuscript.

DATA AVAILABILITY STATEMENT

No data to share for the present paper.

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