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REVIEW

Abnormal synaptic plasticity and impaired cognition in schizophrenia

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Abstract

Schizophrenia (SCZ) is a severe mental illness that affects several brain domains with relation to cognition and behaviour. SCZ symptoms are typically classified into three categories, namely, positive, negative, and cognitive. The etiology of SCZ is thought to be multifactorial and poorly understood. Accumulating evidence has indicated abnormal synaptic plasticity and cognitive impairments in SCZ. Synaptic plasticity is thought to be induced at appropriate synapses during memory formation and has a critical role in the cognitive symptoms of SCZ. Many factors, including synaptic structure changes, aberrant expression of plasticity-related genes, and abnormal synaptic transmission, may influence synaptic plasticity and play vital roles in SCZ. In this article, we briefly summarize the morphology of the synapse, the neurobiology of synaptic plasticity, and the role of synaptic plasticity, and review potential mechanisms underlying abnormal synaptic plasticity in SCZ. These abnormalities involve dendritic spines, postsynaptic density, and long-term potentiation-like plasticity. We also focus on cognitive dysfunction, which reflects impaired connectivity in SCZ. Additionally, the potential targets for the treatment of SCZ are discussed in this article. Therefore, understanding abnormal synaptic plasticity and impaired cognition in SCZ has an essential role in drug therapy.

Key Words: Schizophrenia; Synaptic plasticity; Synaptic structure; Synaptic transmission; Cognitive dysfunction; Abnormality

Core Tip: Schizophrenia (SCZ) is a severe mental illness that affects several domains of cognition and behaviour. SCZ symptoms are typically classified into three categories, namely, positive, negative, and cognitive. The etiology of SCZ is thought to be multifactorial and poorly understood. Accumulating evidence has indicated abnormal synaptic plasticity and cognitive impairments in SCZ. This article will briefly review abnormalities in synaptic plasticity, including synaptic structure, synaptic plasticity-related genes, neuroplasticity, synaptic transmission, and cognitive dysfunction in SCZ.

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INTRODUCTION

Schizophrenia (SCZ) is a chronic, dangerous psychiatric disorder that affects about 1% of people worldwide. Typically, SCZ, occurring in late adolescence or early adulthood, often results in lifetime disability if not effectively controlled. The symptoms of SCZ are generally grouped into three categories, addressed as follows: Positive symptoms (auditory hallucinations and persecutory delusions), negative symptoms (social withdrawal, self-neglect, loss of motivation and initiative, emotional blunting, and paucity of speech), and cognitive symptoms (problems with attention, certain types of memory, and executive functions)[1]. There are numerous hypotheses postulated to elaborate the pathophysiology of SCZ, including the neurodevelopmental hypothesis and synaptic hypothesis. The synaptic hypothesis involves abnormal synaptic transmission and impaired synaptic plasticity.

Synaptic plasticity consists of structural plasticity and functional plasticity. Various evidence discloses abnormal structural and functional plasticity in the pathogenesis of SCZ. Postmortem studies in the brain of SCZ patients point out that there is a significant decrease in the density of dendritic spines (DSs) and the size of postsynaptic density (PSD) in SCZ compared to healthy controls[2,3]. Similarly, functional imaging has revealed that the expression levels of synaptic structure related genes have changed in SCZ[4,5]. Change in morphology or distribution of synaptic structure is related to synaptic plasticity and contributes to SCZ. Additionally, a mouse model of SCZ induced by MK801 also proves that abnormal structural and functional plasticity can constitute to the etiology of SCZ. MK-801-induced mice display the disruption of long-term potentiation (LTP) and change of excitatory postsynaptic potential[6,7]. Furthermore, LTP-like plasticity deficits may result in impairments of learning and memory[8,9].

Abnormal synaptic plasticity might lead to cognitive impairments, including deficits in learning and memory, attention, and social cognition, in SCZ[9,10]. Cognitive impairments refer to aberrant functional connectivity or transmission. Cognitive deficit is an early warning sign of SCZ and contributes to poor functional outcomes[11]. Conventional antipsychotic drugs targeted by dopamine receptors have beneficial effects on positive symptoms but offer minimal benefit for negative symptoms or cognitive symptoms[12]. Therefore, in-depth research on abnormal synaptic plasticity and impaired cognition in SCZ could help understand the underlying mechanism of SCZ and find new drugs to treat it.

This review will focus on recent advances in the understanding of impaired synaptic plasticity and cognitive dysfunction, including changes in synaptic structure, synaptic plasticity-related genes, dysregulation of synaptic transmission, and disconnection, in SCZ, as well as the potential targets for SCZ.

MORPHOLOGY OF THE SYNAPSE

The synapse is a structure that allows a neuron (or nerve cell) to communicate electrical or chemical signals to another neuron or other target effector cell. There are three common types of synapses, respectively called axodendritic, axosomatic, and axoaxonic (Figure 1). In the mammalian brain, neuronal signals are transmitted by two fundamental types of synapses: The electrical synapse and the chemical synapse[13]. A classical chemical synapse is composed of three main parts: (1) The presynaptic components, enclosing neurotransmitter-filled synaptic vesicles (SVs) and proteins (SNARE complex, Munc13, and Munc18) which promote SV recruitment and neurotransmitters release[14]; (2) The postsynaptic components, containing specific receptors and proteins including scaffolding proteins, neurotransmitter receptors, enzymes, and cytoskeletal components, which receive and transmit signals and regulate the synaptic plasticity[15]; and (3) The synaptic cleft, physical space between the presynaptic and postsynaptic terminals which is 10-20 nm, also called synaptic gap (Figure 1D)[16].

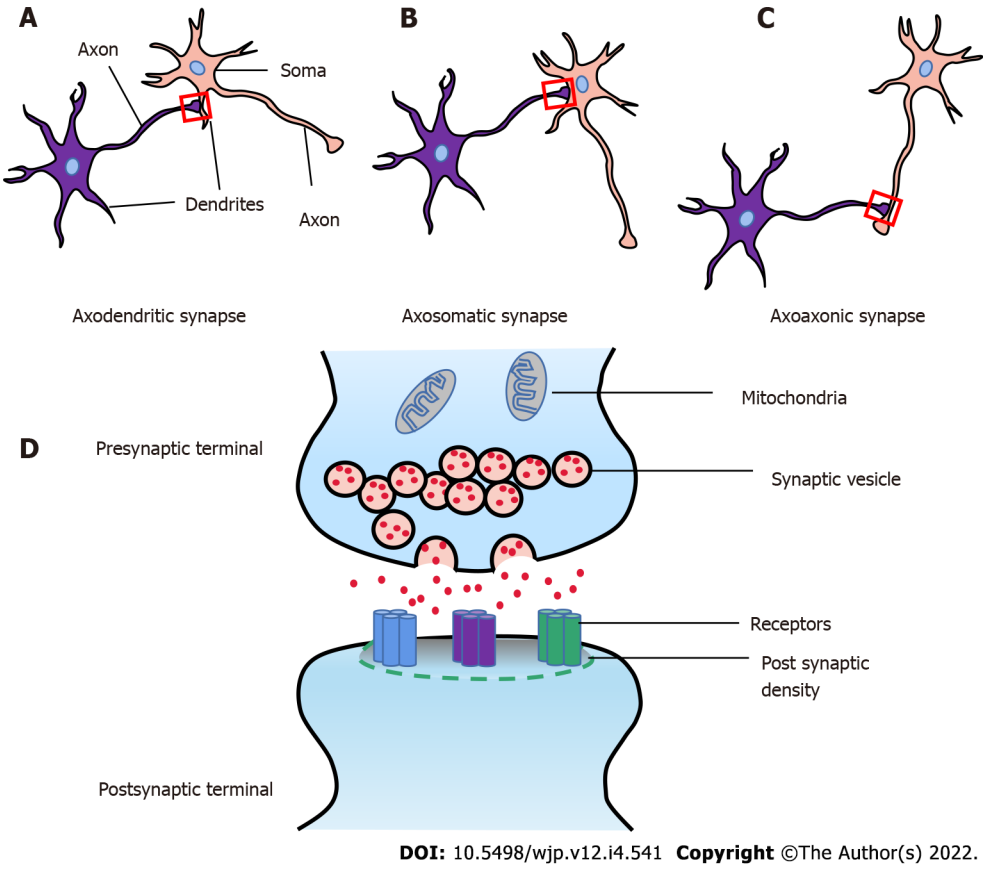

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Figure 1 Types of synapse and structure of a classical chemical synapse. A: Axodendritic synapse; B: Axosomatic synapse; C: Axoaxonic synapse; D: Structure of a classical chemical synapse. A typical chemical synapse usually consists of three parts: (1) Presynaptic membrane including clusters of neurotransmitter-filled synaptic vesicles, mitochondria, and so on; (2) Postsynaptic membrane including neurotransmitter-specific receptors; and (3) Synaptic cleft.

Furthermore, the surface where the presynaptic component and the postsynaptic component are connected is usually called the synaptic interface. It is determined by the width of the synaptic cleft, length of the synaptic active zone, the thickness of PSDs, and curvature of the synaptic interface[17-19]. Changes of synaptic interface closely relate to synaptic function.

In vivo imaging studies have shown that the decreased density of DSs may be a loss of synapse[20]. Spines have a critical role in synaptic transmission. The reduced spines directly correlate with the loss of synaptic function[21,22]. Many factors, including specific gene expression, signal transduction, and new synapse formation, can change synapse level. The total number of synapses is controlled by forming new synapses and pruning old or inappropriate synapses, and finally contributes to synaptic plasticity and memory consolidation[23].

NEUROBIOLOGY OF SYNAPTIC PLASTICITY

Synaptic plasticity (also called synaptic strengths) is the ability of neurons to modify synaptic strength in response to external stimuli. During this process, the structure and function of the synapse are highly dynamic.

Structurally, synaptic plasticity is characterized by the insertion or retention of neurotransmitter receptors, especially AMPAR, into the postsynaptic membrane. Many factors, including the size of DS, the pool of SVs, the areas of active zone, and the PSD, may influence synaptic plasticity[24-26]. Functionally, LTP and long-term depression (LTD) are two forms of synaptic plasticity. There are usually two LTP types, namely, NMDA receptor-dependent LTP and mossy fibre LTP (a cAMP-dependent presynaptic form of plasticity)[27]. The activation of NMDA receptors and increased calcium (Ca^{2+}) concentration are essential for the induction of NMDA receptor-dependent LTP[28,29]. Noteworthy, the spine Ca^{2+} signal is required to trigger LTP[30,31]. Thus, calcium/calmodulin-dependent protein kinase II (CaMKII) has an important role in NMDA receptor-dependent LTP. Besides, various kinases, including protein kinase C, the mitogen-activated protein kinase, and the tyrosine kinase Src, have been implicated in LTP induction[32-34]. Interestingly, some forms of LTP can only maintain 30-60 min, but some can last a very long time, from several hours to days, even for many weeks. The possibilities for the longer-term maintenance of LTP is involved in synaptic structural

remodeling, increased spines size, and enlargement of PSD[35,36].

In summary, synaptic structure, AMPAR trafficking, and DS dynamics are critical for the maintenance of synaptic plasticity.

ROLE OF SYNAPTIC PLASTICITY

Synaptic plasticity in learning and memory

The formation of memory involves four processes: Encoding, storing, consolidating, and retrieving information. Learning is viewed as the acquisition or encoding of the information to memory. The core hypothesis of synaptic plasticity and memory is as follows: Activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation, and is both necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which plasticity is observed[37].

Changing the strength of synaptic connections is a prime process underlying learning and memory formation. Accumulative studies suggest that synaptic plasticity is necessary for learning and memory. The induction of synaptic plasticity requires NMDAR activation. NMDAR1 knockdown mice show deficit in spatial memory in the hippocampus[38]. Besides, synaptic plasticity may contribute to declarative and relational memory[39], sequence learning[40], motor learning[41,42], and perceptual learning at sensory cortex synapses[43]. The traditional view is that fast learning requires more robust synaptic changes[44]. However, some studies suggest that weak synaptic plasticity can support fast learning[45]. Synaptic plasticity has a requisite role in learning and memory across many regions of the brain.

Synaptic plasticity in brain maturation

Human brain maturation is a complex, dynamic, and lifelong process. Billions of cells proliferate, migrate, and maturate during early development, which leads to a brain with billions of neurons at birth, finally forming connections. As children become teenagers, the brain dynamically strengthens or weakens connections in response to environmental input[46]. Simultaneously, neural maturity is increased with age across various brain regions, including primary sensory, motor, associative learning, and cognition function[47]. The prefrontal cortex (PFC) is the last brain region to mature and can mediate executive function such as goal planning, working memory, and guided behavior[48].

Post-mortem studies suggest that the synaptic densities increase rapidly in the visual and auditory cortices, with a maximum of near 3 mo followed by pruning until the age of 12 years[49]. However, synaptic density in the PFC reaches the maximum during childhood, up to 150-200 percent of its adult level. Interestingly, synaptic elimination lasts to mid-adolescence in the PFC[50]. Furthermore, evidence shows that synaptic strength is reduced in the developing brain because it presents synaptic pruning [51]. The specialized and functionally-connected neural circuits accompany regional changes. Additionally, changes in brain volume occur in SCZ. Several reports suggest reducing cerebral cortical volume at premature birth compared to infants born at term[52]. Similarly, there are linearly decreased cortical gray matter and increased white matter across ages 4 years to 12 years[53,54]. In a word, the change of synaptic strength has an influential role in brain maturation and maintenance of a functional neuronal circuit.

IMPAIRED SYNAPTIC PLASTICITY IN SCZ

Abnormal structural plasticity in SCZ

Synaptic plasticity is mediated by structural changes (elongation, contraction, and shape changes) of DSs. DSs are tiny, actin-rich protrusions from the dendritic shaft of various types of neurons. Most of the excitatory synapses are on DSs. Postmortem studies suggest that the density of DSs is reduced in brain tissue of individuals with SCZ, including the neocortex (especially in layer deep 3) and hippocampus, while it may be increased in the dorsal striatum[3,55,56]. Moreover, reduced number of spines and decreased length of basilar dendrites have been observed in SCZ[3]. Deficits in DSs may contribute to the impairment of synaptic plasticity in SCZ.

DSs possess specialized subdomains, including PSD, scaffolding proteins, signal transduction molecules, ion channels, and cytoskeleton components. Under the electron microscope, PSD appears as a regular, dense band about 25 nm to 50 nm thick in the postsynaptic membrane. PSD has essentially different roles in the process of LTP formation[57]. Postmortem study demonstrates a drastic reduction of PSD in the nucleus accumbens in SCZ, especially in asymmetric synapse[2]. The alteration of the synaptic ultrastructure may result from overstimulation of the excitatory synapse. Thus, the alteration of PSD may contribute to SCZ.

Impaired LTP-like plasticity in SCZ

LTP and LTD are two primary forms for studying synaptic plasticity. Many factors, including transmitter release and NMDAR function, can affect LTP[58,59]. The dopaminergic or serotonergic systems can also modulate LTP. Impaired LTP and LTD-like plasticity have been reported in SCZ[60,61].

Evidence has shown altered LTP-like plasticity in SCZ compared to healthy subjects[61,62]. Furthermore, NMDAR antagonists (phencyclidine, MK801, and ketamine) can induce SCZ-like symptoms in healthy individuals[63,64]. Studies reveal NMDAR hypofunction in SCZ[65]. Those changes are involved in excitation and inhibition imbalance, controlled by excitatory neurotransmission glutamate and inhibitory neurotransmission gamma-aminobutyric acid (GABA). Electrophysiological recordings reveal that MK801 treatment can significantly suppress the frequency of miniature excitatory postsynaptic current/miniature inhibitory postsynaptic current ratio of layer (L) 2/3 PNs[66]. Neurogranin, a calmodulin-binding protein, modulates LTP in the hippocampus. The lower level of neurogranin results in hypo-phosphorylation of NMDAR subunit NR2A and finally contributes to NMDAR current decay[67]. Maybe, NMDAR hypofunction accounts for the lack of associative LTP-like plasticity in patients with SCZ.

Ca^{2+} entry is another crucial factor for the induction of LTP-like plasticity. The voltage-gated calcium channel is critical for mediating intracellular Ca^{2+} entry, especially the $Ca_v1.2$ or $Ca_v1.3$ channel. Clinical findings reveal the alteration of intracellular calcium homeostasis in SCZ[68]. Calcium concentration level increases in the cerebrospinal fluid (CSF) of patients with SCZ when acute psychotic symptoms are in remission[69]. It means a positive correlation between SCZ and calcium dysregulation. Therefore, dysregulation of calcium concentration is responsible for changing neuronal excitability and LTP-like plasticity.

Aberrant plasticity-related genes in SCZ

Gene expression studies, including microarray, have discovered the aberrant expression of synaptic plasticity-related genes in SCZ, such as GAP43 and PSD95. GAP43 is a phosphoprotein of the presynaptic membrane that regulates the growth state of axon terminals. Several postmortem studies show reduced GAP43 levels in the frontal cortex and the hippocampus of patients with SCZ[70,71]. What's more, PSD95 is the most abundant protein in the postsynaptic membrane. Postmortem studies show decreased PSD95 protein and mRNA expression levels in SCZ[72,73]. Interestingly, PSD95 can directly interact with ARC or IL1RAPL1 to regulate spine density and function[74,75]. Besides, TAOK2 kinase could directly phosphorylate Septin7 to regulate PSD95 stability and DS maturation[76]. The PSD proteins can directly reflect the number of synapses.

Additionally, some genes regulate the development and function of neuronal synapses. KIF3B, a member of the kinesin superfamily proteins, supports the NR2A/APC complex transport. Its dysfunction relates to SCZ[77]. The dynamic regulation of NR2A and NR2B is critical to the function of NMDAR, which has a substantial role in regulating synaptic plasticity. Besides, CaMKII, ARP2/3, Arc, and PI4KA affect NMDAR function and mediate Ca^{2+} entry[78]. A recent study reports that an envelope protein encoded by human endogenous retrovirus type W (also called syncytin-1) regulates Ca^{2+} entry *via* activating the TRPC3 channel[79], indicating that syncytin-1 may also regulate the development and function of neuronal synapses. Intriguingly, our results show that syncytin-1 can increase the expression of BDNF and IL-6 in SCZ[80,81]. BDNF, an essential member of the nerve growth factor family, regulates synapse formation and contributes to impaired plasticity in SCZ[82]. These data predict that syncytin-1 may participate in the regulation of synaptic plasticity.

In summary, abnormality of synapse morphology, LTP-like plasticity, and synaptic plasticity-related genes may contribute to the pathogenesis of SCZ.

DYSCONNECTION IN SCZ

The hypothesis of dysconnectivity gives two inconsistent explanations: (1) Robust connectivity: The synapse has not been cleared in time in the process of neural system development; and (2) Weak connectivity: Synaptic connectivity decreases and is responsible for the processing information in the brain involving multi brain regions[83,84]. Impaired connectivity is a failure of proper functional integration within the brain, and the connection between different neuron systems influences the functional integration[85]. Effective and functional connectivity plays a prominent role in brain function. Functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetic resonance imaging (MRI), computer-assisted tomography, and magnetic resonance spectroscopy have been used to study brain structure or function.

With the development of brain imaging technology, impaired connectivity has been observed in SCZ. Evidence suggests that prefrontal-limbic cortices are hyperconnected with the mediodorsal thalamus and ventral parts of the striatum and pallidum by fMRI[86]. Impaired connectivity correlates with cognitive impairments. Additionally, PET reveals that SCZ involves dysfunction of a widely distributed cortico-thalamic circuitry[87].

Moreover, an MRI study shows reduced synaptic connectivity in SCZ[88]. These reductions are widespread in the left fronto-parietal network, lateral and medial visual network, motor network, default mode network, and auditory network. Reduced synaptic connectivity is also present in the first episode of psychosis but appears to progress throughout the disorder[89]. The reduction of synaptic connectivity may disturb brain development, including myelogenesis and synaptic pruning or disruption of maturation of inhibitory neural networks such as GABAergic interneurons[90-93]. Maybe, reduced synaptic connectivity involves impaired γ synchronization and increased excitation/inhibition ratio[94]. In conclusion, impaired connectivity found in the brain of patients with SCZ is related to the cognitive dysfunction in SCZ.

COGNITIVE DYSFUNCTION IN SCZ

Since the "dementia praecox" was proposed, cognitive dysfunction had received extensive attention and research in SCZ. It is until 1970s that Gallhofer proposed cognitive symptoms as the third symptoms of SCZ. Cognitive impairments are in the first episode of SCZ[95]. Those deficits include the speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning problem solving, and social cognitive[96]. Kudo *et al*[97] report that increased MMP-9 levels are associated with cognitive impairments in SCZ. High concentrations of S100B correlates with memory impairments, and the variants of S100B may lead to poor performance in patients with SCZ[98,99].

Cognitive deficits may impair global functioning or contribute to poor functional outcomes in SCZ [11]. A four-year follow-up study shows that first-episode SCZ with severe cognitive impairments has no social functioning improvement, even after therapy[100]. Besides, the function and structure of frontal-limbic brain regions have a meaningful role in functional outcome in SCZ[101]. Conventional antipsychotic drug treatment has minimal benefits on cognitive symptoms in SCZ, and even some may impair certain aspects of cognition, such as attention, short-term memory, and learning. However, second-generation (atypical) antipsychotics, such as clozapine, improve several cognitive function domains, especially attention and verbal fluency in SCZ[102-104]. In summary, cognitive deficits are core symptoms of SCZ and result in severe disability.

CASCADE OF NEUROTRANSMITTER AND CIRCUIT DYSFUNCTION IN SCZ

SCZ is currently considered as a polygenic and multifactorial disorder, involving abnormality of synaptic function and neurotransmission, including dopaminergic pathway, serotoninergic pathway, glutamatergic pathway, GABAergic pathway, cholinergic pathway, and other neurotransmitter pathways, such as norepinephrine (NE) and neurosteroids.

Dopaminergic pathway

Typically, the dopaminergic pathway consists of dopamine synthesis, release, and reuptake. It can activate the downstream signal cascades, which play a critical role in synaptic plasticity (Figure 2A). Dopamine is synthesized from tyrosine through two steps: (1) Tyrosine hydroxylase catalyzes the tyrosine to L-DOPA by hydroxylation; and (2) L-DOPA is converted to dopamine by DOPA decarboxylase[105,106]. Dopamine can be stored into SVs, transported to the presynaptic membrane by the vesicular monoamine transporter 2, and finally released to the synaptic cleft[107]. There are five subtypes of dopamine receptors (DRD1, DRD2, DRD3, DRD4, and DRD5) known to mediate dopaminergic physiological functions. Dopamine receptors, especially DRD2, can couple to Gαi/o protein and modulate the PI3K-Akt signal pathway[108,109]. The PI3K-Akt signal pathway has a critical role in cell survival, proliferation, differentiation, glucose metabolism, and gene transcription[110].

Dopaminergic dysfunction has a prominent role in the development of symptoms of SCZ. High dopamine levels in SCZ support this hypothesis[111]. Postmortem studies have suggested a hyperactive dopaminergic system in SCZ, compared to healthy controls[112]. Nowadays, most antipsychotic drugs target dopamine receptors to block dopamine transmission. Notably, DRD2 is considered as the primary target for antipsychotics to alleviate positive symptoms. Moreover, dopamine transporter and vesicular monoamine transporter are decreased in SCZ. However, increased expression of monoamine oxidase A appears to occur in the substantia nigra of patients with SCZ[113].

Serotonergic pathway

Brain 5-HT plays a crucial role in affect and mood control, memory, reward, and modulation of developmental, physiological, and behavioral processes[114-116]. Typically, 5-HT synthesis needs two enzymes: Tryptophan hydroxylase and DOPA decarboxylase. After synthesizing, 5-HT can be transported into SVs and release to the synaptic cleft. Some 5-HT directly binds to its receptors (HTR1A, HTR1B, HTR2A, HTR4, and HTR6), activates downstream signaling pathways to trigger ion channels, and regulates synaptic plasticity (Figure 2B).

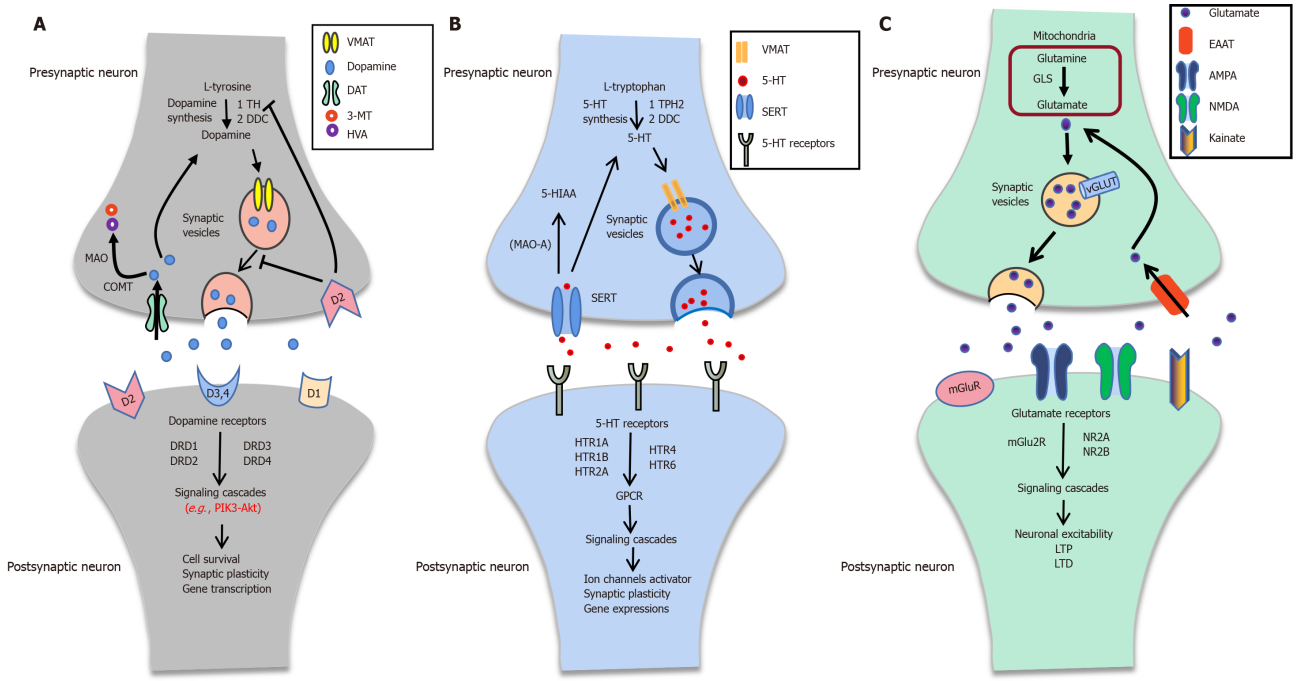

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Figure 2 Neurotransmission in dopaminergic, serotonergic, and glutamatergic neurons. Each pathway step is supplemented with associated genes according to KEGG. A: Dopaminergic pathway. Dopamine is synthesized from tyrosine through two steps: (1) Tyrosine hydroxylase catalyzes the tyrosine to L-DOPA by hydroxylation; and (2) L-DOPA converts to dopamine by DOPA decarboxylase (DDC). Dopamine can be stored into synaptic vesicles by the vesicular monoamine transporters and release to the synaptic cleft. Dopamine as a neurotransmitter, can directly bind to its receptor to activate downstream signaling cascades and influence cell survival, synaptic plasticity, and gene transcription. Besides, dopamine also can be transported back to the presynaptic membrane by the DAT and eliminated. DRD2, an auto-receptor, can inhibit the release of dopamine in the presynaptic membrane; B: Serotoninergic (5-HTergic) pathway. The synthesis of 5-HT needs two enzymes: Tryptophan hydroxylase and DDC. After synthesizing, 5-HT can be transported into synaptic vesicles and release to the synaptic cleft. Some of the 5-HT directly binds to its receptors (*e.g.*, HTR1A, HTR1B, HTR2A, HTR4, and HTR6), activates downstream signaling pathway to activate ion channels, and influences synaptic plasticity and gene expressions, and others are re-uptaken into the presynaptic membrane by the serotonin transporter; C: Glutamatergic pathway. Glutamate is converted from glutamine by phosphate-activated glutaminase in mitochondria and packaged into synaptic vesicles by vesicular glutamate transporters. Sequentially, the glutamate is released to the synaptic cleft and binds to the glutamate receptors, and then activates the downstream pathway or is repacked into presynaptic membrane by excitatory amino acid transporters. Signaling cascade activation might lead to the change of neural excitability and finally has effects on long-term potentiation or long-term depression. MAO: Monoamine oxidase; COMT: Catechol O-methyltransferase; 3-MT: 3-Methoxytyramine; HVA: Homovanillic acid; 5-HIAA: 5-Hydroxy indole acetic acid; EAATs: Excitatory amino acid transporters; 5-HT: Serotonin or 5-hydroxytryptamine; GPCR: G protein-coupled receptor; GLS: Glutaminase; NMDA: N-methyl-D-aspartate receptor; AMPA: α-Amino-3hydroxy-5methyl-4-isox-azolepropionic acid; mGluR: Metabotropic glutamate receptor; LTP: Long-term potentiation; LTD: Long-term depression.

Alteration of serotonin transmission has been implicated in the processes of SCZ. Tryptophan hydroxylase 2 (TPH2), a rate-limiting enzyme for serotonin synthesis, is selectively expressed in the raphe serotonergic neurons[117]. Postmortem studies and single nucleotide polymorphism (SNP) studies show a significant association of TPH2 with SCZ in Han Chinese[118,119]. Additionally, the expression level of SERT (5-HT transporter, also named 5-HTT) is reduced in the frontal cortex of subjects with SCZ[120]. Recently, a SNP meta-analysis shows a strong association between SERT polymorphism and SCZ[121]. Indeed, the 5-HT receptor has an outstanding role in 5-HT transmission. 5-HT1A agonist can directly bind to atypical antipsychotic drugs (AAPDs) to treat cognitive impairments associated with SCZ[122-124]. Maybe as a compensatory mechanism, the expression of serotonin 1A is increased or maybe due to the beneficial effects of AAPDs in SCZ, the 5-HT1A receptor is activated.

Glutamatergic pathway

Glutamate is the principal excitatory neurotransmitter in the central nervous system. Notedly, glutamate is converted from glutamine by phosphate-activated glutaminase in mitochondria and packaged into SVs by vesicular glutamate transporters (VGLUTs). Sequentially, the glutamate releases to the synaptic cleft. It then activates the downstream pathway or is re-uptaken into the presynaptic membrane by excitatory amino acid transporter after binding to the glutamate receptors (Figure 2C). Besides, the cystine/glutamate antiporter system x_c^-, which might exchange cystine for glutamate in a 1:1 ratio, has a vital role in releasing glutamate[125]. The "glutamate hypothesis" was first proposed by Kim *et al*[126]. They found that glutamate levels were decreased compared to healthy controls in CSF with SCZ[126]. The glutamatergic hypothesis of SCZ is based on the NMDAR hypofunction and the abnormality of glutamate transmission in SCZ.

Postmortem brain study shows a decreased expression level of VGLUT1 in the hippocampus of patients with SCZ[127]. However, VGLUT2 protein levels are increased in the inferior temporal gyrus (ITG) of SCZ[128]. The loss of VGLUT activity eliminates vesicular release and glutamatergic neurotransmission and regulates presynaptic quantal size or synaptic plasticity[129]. Postmortem studies have also revealed an increase in EAAT1 and EAAT2 transcripts in Brodmann's area (BA) 10 of subjects with SCZ, but not BA46[130]. Similar results have a relatively high agreement in the thalamus and cerebellar vermis[131,132]. These results indicate that EAAT is involved in glutamate reuptake in SCZ. Furthermore, evidence shows that mRNA expression levels of SLC3A2 and SLC7A11, two system x_c^- subunit genes, are decreased in peripheral white blood cells of SCZ patients compared to healthy controls. Abnormality of system x_c^- is involved in glutamatergic neurotransmission[125]. NMDAR-mediated glutamate transmission has been implicated in cognitive execution in the nucleus accumbens of SCZ[133]. Changes in the mRNA and protein levels of NMDAR subunits have been described in SCZ [134]. Suppressed NMDAR signaling through Src kinase may facilitate presynaptic glutamate release during synaptic activity[135]. In addition, the D-amino acid oxidase activator (DAOA, also called G72) protein, which has an important role in modulating NMDAR signaling, has a strong association with SCZ[136,137]. Those results indicate that alteration of glutamatergic transmission has a meaningful role in SCZ.

GABAergic pathway

Reduced GABAergic neurotransmission is in support of the 'GABA hypothesis' for SCZ[138]. RNA-Seq analysis reveals the disruption of GABA metabolite levels in SCZ[139]. Moreover, postmortem studies suggest that subjects with SCZ have lower mRNA and protein levels of synthetic enzyme GAD67 compared to healthy controls[140]. Lower expression of GAD67 may be a consequence of a deficiency of the immediate early gene Zif268, suggesting a potential mechanistic basis for altered cortical GABA synthesis and impaired cognition in SCZ[141]. GAD67 promoter methylation levels are associated with the SCZ-risk SNP rs3749034 and with the expression of GAD25 in the dorsolateral prefrontal cortex (DLPFC). Alternative splicing of GAD67 may contribute to GABA dysfunction in SCZ[142]. Similarly, the immunoreactivity of GAT1, a protein responsible for the reuptake of GABA, is decreased in SCZ [143]. Furthermore, GAD1 knockout rats exhibit SCZ-related phenotypes, such as cognitive impairments in spatial reference and working memory in the hippocampus[144]. A PET study using [^{11}C] Ro154513 has reported differential expression of GABA-A receptors in SCZ[145]. Therefore, the synthesis and reuptake of GABA are lower in SCZ. These abnormalities of GABAergic neurotransmission are related to cognitive impairments in SCZ.

Cholinergic pathway

Acetylcholine has a vital role in cognitive and behavioural/psychological function. Pharmacologic studies show that central cholinergic activity profoundly affects the storage and retrieval of information in memory. The choline acetyltransferase, a cholinergic function marker, is correlated with the severity of cognitive impairments in the parietal cortex of schizophrenic patients[146]. Furthermore, cholinesterase inhibitors (donepezil or rivastigmine) have positive effects on cognitive dysfunction in SCZ[147, 148]. These inhibitions increase the synaptic concentration of acetylcholine and finally enhance and prolong acetylcholine action on muscarinic and nicotinic receptors in the postsynaptic membrane.

SCZ patients show decreased α4β2 nicotinic acetylcholine receptors (nAChR)[149]. However, the α7 nAChR level is increased in the DLPFC of SCZ patients[150]. Besides, functional polymorphisms of the α7 nAChR have shown genetic linkage in SCZ[151]. Muscarinic receptors, also called the metabotropic muscarinic acetylcholine receptors, have five subtypes (M1-M5 receptors), encoded by the CHRM1-5 genes. Postmortem studies suggest lower CHRM1 levels in the cortex of patients with SCZ[152]. The loss of cortical CHRM1 may be regulated by miR-107 in SCZ[153]. What's more, CHRM1 is involved in memory processes, and blockade of hippocampal CHRM1 demonstrates a deficit in working memory [154]. Together, these results suggest that alterations in the cholinergic pathway may contribute to a breakdown in cholinergic homeostasis and have a key role in the pathophysiology of SCZ, particularly the cognitive impairments.

Other neurotransmitter pathways

Other neurotransmitter pathways, such as NE and neurosteroids, have also been implicated in the cognitive dysfunction of SCZ.

NE is a significant neuromodulator of brain function and neural gain. NE exerts its effects through noradrenergic receptors (α1, α2, and β). The alteration of noradrenergic neurotransmission has been studied for years. It is a consensus that patients with SCZ have higher NE levels than the control group [155,156]. Furthermore, α2-adrenergic receptor antagonist idazoxan has antipsychotic efficacy in the treatment of SCZ, especially the anxiety or depression symptoms[157]. It may be associated with the increased output of DA.

Additionally, the abnormality of neurosteroid transmission also has a crucial role in the pathobiology and symptomatology of SCZ[158]. Both the levels of progesterone and allopregnanolone (ALLO) are decremented in SCZ in a postmortem study[159,160]. Studies suggest that ALLO enhances NMDA

receptor neurotransmission by interaction with σ1 receptors in SCZ[161,162]. What's more, decreased levels of ALLO may modulate GABAergic transmission in the brain and finally lead to impairments of GABAergic function in SCZ[163].

POTENTIAL TARGETS FOR TREATMENT OF SCZ

Most antipsychotic drugs target serotonin-dopamine receptors or serotonin-glutamate receptors, suggesting disarranged neurotransmitter interaction. Newer AAPDs, such as clozapine, olanzapine, and risperidone, have been developed because of their significant effects on dopaminergic receptor subtypes and serotonergic receptors[164]. Interestingly, co-immunoprecipitation studies verify that HTR2A and DRD2 physically interact in HEK293 cells. Furthermore, shreds of evidence reveal that HTR2A and mGlu2 receptors can assemble into a functional heteromeric complex to modulate each other's function [165,166]. The expression of HTR2A is required for phosphorylation of mGlu2R at serine 843 and promotes mGlu2R-modulate G i/o signaling[167]. Therefore, there are potential antipsychotic drugs by targeting HTR2A, DRD2, and mGlu2R. DRD3 was found to be associated with SCZ in a case-control study[168]. Several pharmaceutical studies suggest that DRD1/5 agonists have potential therapeutic effects in SCZ by improving cognitive or negative symptoms[169,170]. What's more, HTR4/6 agonists can improve cognitive symptoms in SCZ. HTR4/6 may be a promising target for treatment of cognitive dysfunction in SCZ[171]. Additionally, sarcosine (a competitive inhibitor of the type 1 glycine transporter) and D-amino acid oxidase (DAAO or DAO) inhibitor can improve the clinical symptoms in SCZ patients. Therefore, glycine transporter and DAO may offer potential therapeutic targets for SCZ [172,173].

There are many other potential targets for the treatment of SCZ. Accumulated pieces of evidence have revealed various susceptibility genes in SCZ, including STAB2, GRIN1, GRIN2A, ARC, BDNF, NRGN, syncytin-1, and others[67,81,174]. Interestingly, many of those genes appear to be related to the control of synaptic plasticity and cognitive impairments in SCZ. BDNF plays a principal role in regulating synaptic organization, neurotransmitter synthesis, and the maintenance of synaptic plasticity[175]. Data from our lab provide evidence that syncytin-1 can regulate the expression of BDNF and DISC1. Furthermore, GNbAC1, a monoclonal antibody targeting syncytin-1, has been implicated in the treatment of multiple sclerosis and type 1 diabetes[176,177]. Thus, syncytin-1 is a promising therapeutic target for SCZ in the future.

CONCLUSION

Accumulated shreds of evidence indicate that changes in the morphology of synapses have a vital role in the incidence of SCZ. The potential role of synapse in SCZ appears much more complicated. In conclusion, the synapse can be involved in three aspects as follows: (1) The change of synaptic plasticity (*e.g.*, change in the dendrite spines, PSD, and alteration in LTP and LTD); (2) The abnormalities in neurotransmission (*e.g.*, dopaminergic transmission, serotoninergic transmission, and glutamatergic transmission); and (3) The impairment of cognition (*e.g.*, disconnection).

Impaired synaptic plasticity contributes to cognitive dysfunction in SCZ. These dysfunctions include abnormal brain connectivity and functional outcomes. With the development of brain imaging technology, research on cognitive impairments should do not focus on a single gene or brain regions but on neural circuits or brain networks to study the underlying mechanism in SCZ. SCZ is a complex disease, and there are still no available antipsychotic drugs to treat all symptoms of SCZ or accompany little side effects. Finding potential antipsychotic drug targets will help identify and develop novel therapeutic agents with fewer side effects.

FOOTNOTES

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REVIEW

Anorexia nervosa: Outpatient treatment and medical management

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Abstract

Anorexia nervosa (AN) is a disabling, costly and potentially deadly illness. Treatment failure and relapse are common after completing treatment, and a substantial proportion of patients develop severe and enduring AN. The time from AN debut to the treatment initiation is normally unreasonably long. Over the past 20 years there has been empirical support for the efficacy of several treatments for AN. Moreover, outpatient treatment with family-based therapy or individual psychotherapy is associated with good outcomes for a substantial proportion of patients. Early intervention improves outcomes and should be a priority for all patients. Outpatient treatment is usually the best format for early intervention, and it has been demonstrated that even patients with severe or extreme AN can be treated as outpatients if they are medically stable. Inpatient care is more disruptive, more costly, and usually has a longer waiting list than does outpatient care. The decision as to whether to proceed with outpatient treatment or to transfer the patient for inpatient therapy may be difficult. The core aim of this opinion review is to provide the knowledge base needed for performing safe outpatient treatment of AN. The scientific essentials for outpatient treatment are described, including how to assess and manage the medical risks of AN and how to decide when transition to inpatient care is indicated. The following aspects are discussed: early intervention, outpatient treatment of AN, including outpatient psychotherapy for severe and extreme AN, how to determine when outpatient treatment is safe, and when transfer to inpatient healthcare is indicated. Emerging treatments, ethical issues and outstanding research questions are also addressed.

Key Words: Anorexia nervosa; Outpatient treatment; Medical management; Outpatient psychotherapy; Inpatient healthcare

Core Tip: Outpatient psychotherapy is the mainstay of treatment of anorexia nervosa. Both early intervention and healthcare for severe and enduring anorexia nervosa are mainly performed in outpatient clinics. Even in severe and extreme anorexia nervosa outpatient psychotherapy is an alternative to inpatient treatment when the patient is medically stable. Medical management is essential for safe outpatient therapy. In this opinion review essentials in outpatient healthcare and medical management are discussed. Emerging therapies and outstanding research issues are addressed.

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INTRODUCTION

Anorexia nervosa (AN) is characterized by starvation, malnutrition, fear of weight gain and/or a disturbed body image, and severe dietary restriction or other weight-loss behaviors (*e.g.*, purging, excessive physical activity). There are two subtypes of this condition: binge eating with purging (or only purging), and food restricting only[1,2]. Patients usually have a low body mass index (BMI), but some patients with rapid weight loss have a clinical picture of AN with a BMI within the normal range[3]. In addition, cognitive and emotional functioning are often markedly disturbed[4,5]. The prognosis is poor for a substantial proportion of patients[6], and mortality rates are high[7]. The comparative efficacy of available treatments is described in recent systematic reviews and meta-analyses[1,4]. The core aim of the present opinion review is to present an overview of the scientific essentials for AN outpatient treatment, including how to assess and manage the medical risks of AN, and how to decide when transition to inpatient care is indicated. Emerging therapies and outstanding research questions are addressed.

DIFFERENTIAL DIAGNOSIS

The diagnostic criteria for AN in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) are provided in Table 1[2]. Diagnosing AN is usually straightforward, although sometimes the use of additional informants such as parents is necessary[4].

Inflammatory bowel disease (Crohn's disease or ulcerative colitis), malignancies, thyrotoxicosis and diabetes can present a clinical picture similar to AN. In rare cases AN can be mimicked by a cerebral tumor including pituitary adenoma[4]. Patients with severe depression can experience weight loss due to loss of appetite or a belief that they do not deserve food. A patient with schizophrenia might avoid food due to various delusions[4]. Avoidant/restrictive food-intake disorder (ARFID) was initially regarded as a disorder of childhood, but is now regarded as an age-neutral disorder[4]. Core symptoms are food avoidance or restriction (volume or variety), together with weight loss or faltering growth, nutritional deficiencies, dependence on nutritional supplements for sufficient intake, and/or psychosocial impairment[4]. Although patients with ARFID do not present with the concerns about weight and body shape typically associated with AN[8], they are susceptible to the same medical complications[4,9].

EPIDEMIOLOGY

Approximately 92% of individuals affected by AN are female[10], but all genders, sexual orientations and ethnicities are affected[11]. The most common age of onset is 15-25 years[12]. The age of onset appears to be decreasing[6,13,14]. The incidence is low in children aged 4-11 years, but it increases significantly with age above 11 years[6]. The restricting subtype of AN is associated with earlier onset and greater likelihood of crossover to the binge-eating/purging subtype[15]. Onset after the age of 30 years is rare[13,16].

The estimated prevalence of AN among young females is 0.3%[13,17], and it affects up to 4% of females and 0.2% of males during their lifetime[17,18].

Time-trend data suggest that the incidence of AN in Europe increased from the 1930s to the 1970s. This might have been due to improvements in the detection rate of persons with AN, but it might also reflect a true increase. In the 1960s another beauty ideal became more widely adopted, as represented by very thin models such as the supermodel Twiggy. It appears that the incidence of AN in Europe was

Table 1 Diagnostic criteria, subtypes and severity of anorexia nervosa

Diagnostic variable	
Diagnostic criteria	(1) Restriction of energy intake relative to requirements in anorexia nervosa leads to significantly low body weight for the patient´s age, sex, developmental trajectory and physical health. Significantly low weight is defined as a weight that is less than the minimal normal weight or (in children and adolescents) less than the minimum expected weight; (2) Intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain, even though the patient has a significantly low weight; and (3) Disturbance in the way in which one´s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight
Subtype designation	Restricting subtype: During the past 3 mo, the patient has not engaged in recurrent episodes of binge-eating or purging behaviour (*i.e.* self-induced vomiting or the misuse of laxatives, diuretics or enemas). Weight loss is primarily through dieting, fasting or excessive exercise, or all of these methods; Binge-eating/purging subtype: During the past 3 mo, the patient has engaged in recurrent episodes of binge-eating or purging behaviour (*i.e.*, self-induced vomiting or the misuse of laxatives, diuretics or enemas)
Current severity	Mildly severe low body weight is defined as BMI > 17.00 kg/m^2; Moderately severe low body weight is defined as a BMI of 16.00-16.99 kg/m^2; Severe low body weight is defined as a BMI of 15.00-15.99 kg/m^2; Extremely severe low body weight is defined as BMI < 15.00 kg/m^2[1,2]

All three diagnostic criteria are required for the diagnosis anorexia nervosa. BMI: Body mass index.

stable from 1970 into the 21st century[19], but the global incidence of AN appears to be increasing, particularly in Asia and the Middle East[20,21]. However, the incidence of AN remains low in Africa and among African American females in the USA, in Latin America, and among Hispanics/Latinos in the USA[19]. These observations may reflect both genetic and cultural etiological factors. A large-scale national health survey in South Africa revealed that despite a high mean BMI of 29.0 kg/m^2, more black African females were happy with their current weight and fewer attempted to lose weight, compared with females of other ethnicities[19,22]. A study involving the Caribbean Island of Curacao found no cases of AN among the mainly black population, while the incidence in the white population was similar to that in the United States and the Netherlands. That study was performed when the cultural influence of North America and Europe was increasing with the development of an affluent minority and relatively poor majority[23]. Studies involving Hispanics/Latinos in the United States found that they had fewer concerns about weight gain than did their non-Hispanic white peers, leading to fewer cases of AN[24]. This seems to be related to a body ideal of a "curvier" shape and higher body weight compared with the ideals in Western countries[25,26]. Case series of males with AN in Western societies indicate that they display many of the same characteristics and clinical course as females with AN[27]. AN in males has been reported in non-Western societies, but few cross-cultural data are available on the incidence and prevalence of AN among males[28,29].

RISK FACTORS AND DEVELOPMENT

The etiology of AN is complex and involves genetic and neurobiological factors[30], and a range of psychological risk factors has been identified, such as childhood anxiety disorders, trauma (*e.g.*, sexual assault, physical abuse, neglect), early feeding problems, temperamental traits such as inhibition, perfectionism and harm avoidance[31]. In addition, living in a society in which a high value is placed on thinness, including occupations that require a lean physique and perfectionism (*e.g.*, sports and modelling), seems to be associated with an increased risk of AN[1,32-34]. Genetic studies indicate that genes coding for metabolic factors seem to play an important role in the development and maintenance of AN. The aspects of AN as a metabo-psychiatric disorder are further discussed in the section below on emerging therapies and outstanding research issues.

Most AN patients report that they started losing weight by voluntary dieting, but in some patients the weight loss is caused by depression, trauma, excessive exercise, a gastrointestinal disorder or protracted infection. If the initial weight loss is voluntary, the patient usually has a positive experience during the first mo. However, over time they will find it increasingly difficult to eat normally, and a normal meal can induce discomfort, anxiety or even panic reactions. The patient gradually becomes preoccupied with body weight and body shape. Negative experiences from trying to eat normally lead patients to eating too little. Food intake is further decreased in times of stress, and even everyday stressful experiences may induce a further reduction in food intake. Thus, patients enter a vicious cycle of reduced food intake with increasing overvaluation of shape and weight, and further reduction of food intake. Treatment becomes more difficult when these psychological maintaining mechanisms are established. The vicious cycle appears to include both psychological and somatic factors that are closely related to nutritional status (see Figure 1).

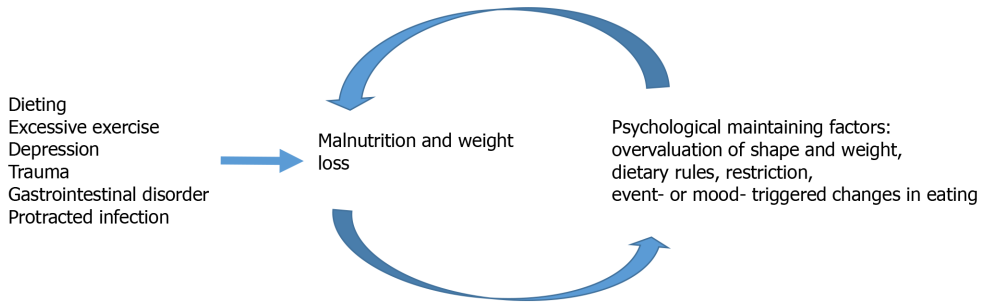

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Figure 1 Illustration of how anorexia nervosa may develop in most patients. Dieting, excessive exercise, depression, trauma, gastrointestinal disorder or protracted infection induce weight loss and malnutrition. In susceptible individuals the malnutrition causes the development of maintaining psychological mechanisms, which in turn decrease food intake and increase malnutrition. The malnourished patients enter a vicious cycle of reduced food intake with increasing overvaluation of shape and weight, they often establish dietary rules in order to decrease food intake and restrict their food intake. Everyday stressful experiences may induce event - or mood triggered further reduction in food intake.

PRIMARY PREVENTION

Research into the primary prevention of eating disorders (EDs) is in its early stages. A meta-analysis[35] concluded that there are promising strategies for universal prevention (targeting whole populations) as well as the selective prevention of EDs (targeting individuals showing specified risk factors), but not for indicated prevention (early detection and intervention for individuals with symptoms below the diagnostic level of EDs). However, most studies were found to have a high risk of bias, which demonstrates the methodological challenges of this research. The picture is even more complicated when looking specifically at AN. Stice *et al*[36] reviewed known risk factors to target in preventive interventions. They highlighted the challenge that risk factors predicting other EDs (body dissatisfaction, negative affect, thin-ideal internalization, perceived pressure for thinness, dieting and family support deficits) do not consistently predict AN. Existing prevention programs tend to target these risk factors, and therefore they might be less effective in preventing AN. The only risk factor that spans the full spectrum of EDs, including AN, is impaired psychosocial functioning. An additional risk factor for AN is low BMI. This situation prompted Stice *et al*[36] to argue that AN-specific preventive strategies should target psychosocial functioning and healthy weight gain. However, previous universal prevention programs have demonstrated little or no effect on the prevalence of AN. A long-term effectiveness study of a school-based primary prevention program for AN in Germany found an effect on body self-esteem but not on disordered eating. However, that study exhibited implementation difficulties, including problems with maintaining the sample size[37]. Primary prevention in smaller populations with a high risk of an ED seems to exert some effects. An intervention designed to prevent the onset of EDs among adolescent athletes through a 1-year intervention program prevented the onset of EDs and reduced symptoms associated with EDs relative to assessment-only control athletes. However, the small number of ED patients in that study prevented a subgroup analysis of the effect on the prevalence of AN[36,38].

A recent study reviewed the evidence for the early detection of individuals fulfilling diagnostic criteria, which is an aspect of secondary prevention[39]. Those authors found evidence that educational interventions targeting professionals (*e.g.*, from medical, educational or sports environments) are somewhat effective. The case for early detection is very strong, since many studies have demonstrated that the risk of severe and enduring anorexia nervosa (SE-AN) increases with the duration of untreated illness[40]. Until more evidence on primary prevention of AN is available, it seems prudent to focus efforts and healthcare costs on early detection and ease of access to treatment.

PROGNOSIS AND MORTALITY

Rates of recovery from AN at 1- to 2-year follow-ups with the best available treatments lie in the range of 13-50% across age groups[41,42]. Among the patients who complete psychotherapy the relapse rates are ranging from 9% to 52%, with most studies finding rates higher than 25%[43]. The average duration of illness with AN is about 6 years[12]. The long-term course is heterogeneous, with 20-year longitudinal studies finding that 30%-60% of patients will experience full remission, while 20% will have enduring illness and the remainder will have residual symptoms[43,44].

In a meta-analysis of 36 studies published between 1966 and 2010, the standardized mortality ratio for patients with AN (the percentage of observed deaths among patients with AN divided by the percentage of expected deaths in the population of origin) was 5.9[7]. One in five individuals with AN

who died had committed suicide[7]. However, these data were often derived from patients admitted to hospitals, and early intervention and active engagement might have reduced the prevalence, need for hospitalization and mortality[4,14]. No mortality was observed in a cohort of 51 patients with AN recruited from all individuals born in 1985 in Gothenburg, Sweden who were followed for 30 years[45]. Although these observations were made in a small cohort of young patients, they might indicate that early intervention and structured follow-up are associated with low mortality.

COMORBIDITIES

Both psychiatric and somatic comorbidities are common in AN. The most common psychiatric comorbidities are mood and anxiety disorders, obsessive-compulsive disorders, personality disorders, substance-use disorders and neurodevelopmental disorders such as autism spectrum disorder or attention-deficit hyperactivity disorder[4]. Comorbid disorders tend to worsen the prognosis of AN because they interfere with treatment response[46-49]. Suicidal behaviors and ideation are markedly increased in patients with ED[50,51]. Type 1 diabetes is sometimes a challenging comorbidity, since the omission of insulin in order to lose weight can induce severe complications, including recurring ketoacidosis and rapid development of neurological, retinal and renal complications, and is associated with a significantly increased mortality rate compared with AN without type 1 diabetes[52].

THE CLINICAL INTERVIEW AND THE PHYSICAL ASSESSMENT

Since most patients with AN should be treated as outpatients, the assessment should determine whether outpatient treatment is safe. A clinical interview is essential for risk assessment. Ascertaining the duration and severity of the patient's ED may help to identify likely complications. Assessment of nutrition should include information about the intake of bread and similar thiamine-containing nutrients, the intake of meat and fish and other zinc-containing nutrients, and whether the patient has a varied or monotonous diet with the associated risk of multiple deficiencies[53,54]. Information about physical capacity compared with friends or relatives of the same age should be obtained. The clinical interview should also assess whether the patient has excessive exercise, vomiting and use of laxatives or other medications, including those that aim to increase metabolism (*e.g.*, thyroxine), or herbs or other substances that may have metabolic or diuretic effects[55].

The presence of purging behaviors is sometimes difficult to assess, and corroborative sources of data should be obtained whenever possible. Information about past eating disorder treatment including previously diagnosed complications is also valuable[50]. Anamnestic information regarding attacks of dizziness, syncope, or near-syncope warrants the acquisition of more detailed anamnestic information about possible arrythmia and other causes of the attacks such as hypoglycemia or hypotension. Information regarding exercise (especially excessive exercise), vomiting or other purging activity, pulse rate during or before the attack, and data on altered medication can shed light on possible underlying mechanisms. In particular, recent onset of symptoms suggestive of cardiac arrythmia is important because refeeding might alter the electrolyte balance and further worsen unstable arrythmia. Chest pain and attacks of dyspnea could be related to pneumothorax or cardiovascular disease. The malnutrition in AN is associated with pulmonary changes that may predispose to spontaneous pneumothorax[56]. Patients with severe or extreme AN may have several potentially lethal complications, and these patients should be assessed by a physician with experience in extreme AN before outpatient treatment is commenced.

A physical examination should be performed in a sufficiently warm room and undressing should be performed gradually and respectfully to allow examination of the chest with auscultation of lungs and heart, including searching for systolic murmur in the left axilla that indicates mitral-valve insufficiency. Gentle palpation of the abdomen can give valuable information on the location of any abdominal pain, and whether the pain is referred. Palpation and percussion can reveal distension of the GI tract and other parts of abdomen including tendency to gastric retention. Arms and legs should be examined to assess the peripheral circulation, dehydration, peripheral oedema and pitting. Balance can be assessed by asking the patient to stand on one foot, and simple tests of coordination can reveal the risks of falling and fractures. Problems with coordination and balance can be related to malnutrition-induced cerebellar dysfunction or proximal myopathy, which is a common problem in severe malnutrition. This myopathy can be significantly increased during refeeding and can be associated with increased risk of falling[34].

It might be difficult to measure the blood pressure properly due to thin arms, but in patients with symptoms of orthostatic hypotension, valuable information can be revealed by using a blood-pressure cuff for children. Palpation of the pulse can give information about the heart rate, pulse pressure and dehydration, and the tendency for severe hypotension, which causes a very thin pulse wave with relative tachycardia[57]. Resting tachycardia is unusual and may be indicative of a superimposed infection or other complication[58]. The usual signs of infection (fever and elevated white blood cell count) may not be present in AN. A lower threshold to evaluate for an infection should be followed[57].

Examination of the teeth can reveal erosions, indicating possible vomiting with risk of electrolyte disturbances[59].

Blood tests in AN (especially restricting AN) can be normal or close to normal even when the patient is at risk of lethal arrythmia or other severe complications of treatment. Therefore, using blood tests alone without comparing with the clinical picture is not adequate for risk assessment. Assessment of patients with extreme AN (BMI < 15 kg/m^2) should be performed in collaboration with a physician with experience in extreme AN as this group of patients may have a large number of complications[57,60].

TREATMENT

Outpatient psychotherapy is the mainstay of treatment for AN, as it is less costly and disruptive than other, more intensive levels of care[61,62]. A proportion of patients will need inpatient psychotherapy or supportive care. Research data to guide choices among types of psychotherapy for outpatient and inpatient treatment are limited and disputed[1]. AN remains difficult to manage since patients are often challenging to engage, and outcomes are often poor, even in those who agree to commence treatment [61]. However, over the past 20 years there has been empiric support for the efficacy of several treatments, mainly in the outpatient setting, and thanks to an improved understanding of the psychological mechanisms that maintain them, manualized treatments for children, adolescents and adults with AN have been developed.

The decision regarding whether to proceed with outpatient treatment or to transfer a patient for inpatient therapy may be difficult, especially in non-specialist or general psychiatry settings. The feasibility of outpatient psychotherapy requires containment of concerns regarding the short- and long-term somatic consequences of malnutrition and monitoring of medical safety needs. The patient's medical and psychiatric stability, AN severity, age and duration of illness must be considered during treatment decision-making[34]. Psychopharmacological medications are generally ineffective for promoting weight gain, reducing AN-related depressive symptoms or preventing relapse in AN[1]. However, there is some preliminary evidence for the use of atypical antipsychotics for adolescents to support the acute phase of renourishment[63]. Overall, medication plays a very limited role in the treatment of AN[1,64-66].

Early intervention improves outcomes, and so the rapid commencement of specialized treatment for EDs is essential[4,67,68]. The duration of untreated AN before treatment initiation varies, but multiple studies have found that adults and adolescents had AN for a mean of 30 mo before treatment was initiated[4]. The First Episode Rapid Early Intervention for Eating Disorders (FREED) study found that the duration of untreated AN in patients aged 16-25 years could be significantly reduced by implementing an early intervention service model and care pathway for young adults with EDs[69]. In addition, the proportion of patients taking up treatment was significantly higher among FREED patients than among those who received treatment as usual (TAU)[69].

Treatment of children and adolescents

Family-based treatment (FBT) is the most empirically supported intervention for children and adolescents with AN[4,29,70,71]. In general, FBT does not align with a particular therapeutic approach, but instead integrates techniques from a variety of schools of psychotherapy, including systemic, strategic, narrative and structural types of family therapy[72]. The overall philosophy of FBT is to empower parents to help their child to overcome a disease that is beyond his/her own control. The family is viewed as a resource and the child or adolescent with AN is seen as embedded in the family and temporarily regressed, and parental involvement in therapy plays a pivotal role in treatment success[72].

Six randomized, controlled trials (RCTs) have assessed the efficacy of manualized FBTs for AN in adolescents. Manualized FBTs have been compared with a single individual therapy (*i.e.* adolescent-focused therapy) in only one RCT. In that trial, FBT was not significantly more efficacious than was adolescent-focused therapy at the end of treatment, but it was more effective for facilitating full remission at follow-up[61,73]. The findings of a Cochrane review suggest that the evidence favoring family-based interventions over standard treatment or other psychological approaches is not robust [74]. This opinion has been criticized partly because studies of questionable validity were not excluded from the Cochrane review and because the study had inadequate statistical power[75]. FBT is recommended in several clinical guidelines[29,62,76] on the basis of evidence of remission rate, faster weight gain and less reliance on the young patient's own motivation and ability to change their symptomatic behaviors.

Several modifications of standard FBT have been tested. One of these is Parent-Focused Family Therapy, a type of FBT in which most sessions only involve the parents. According to one high-quality RCT, this modality is as effective as traditional FBT, where the family is seen together[29,77]. Another modality of family therapy that has been adapted to treat AN is multifamily therapy, which draws on the conceptual principles of FBT, applying them to groups of typically five to seven families in extended whole-day sessions, initially over four consecutive days. The presence of other families and the intensity

of the contact creates a powerful treatment context wherein families learn from each other, share their experiences and gain multiple perspectives on the problems they face. The group context also helps to reduce the sense of isolation and stigmatization that is often experienced by families living with an ED [78]. Another high-quality RCT compared systemic family therapy with FBT and found no significant differences in remission rates; however, the rate of weight gain was greater and the need for hospitalization was significantly lower in the FBT group[79].

While parental involvement is effective and often necessary to bring about changes in children and adolescents with AN, it does come at a considerable cost for the families. Parents may find the task of renourishment in the face of strong emotional reactions from their child daunting[80,81], and the intensive care required may be an economic burden for parents since it may require them to take time off from work. Regardless of which mode of FBT is chosen, monitoring of the patient's somatic condition is necessary in order for parents to know that their child is safe while they struggle to learn how to manage, for example meal support, and for the family therapist to support the agency of the parents. Furthermore, although parents receiving FBT are supported to rely on their own experience when making feeding choices, they may need dietary advice on how to increase the energy density of the meals they provide to affected children. Consequently, easy access to multidisciplinary support helps parents and therapists to provide effective outpatient psychotherapy. It is important that all team members, *e.g.*, the physician in charge of somatic assessment, understand the principles of parent empowerment, as described by Katzman *et al*[82].

Treatment of adults

Data to guide choices among types of psychotherapy for adults remain inadequate and disputed[1]. The guideline from the National Institute for Health and Care Excellence (NICE) on the recognition and treatment of EDs recommends that the first-line treatments for adults consist of structured individual therapies that focus on EDs, including individual cognitive behavior therapy (CBT) with an eating disorder focus (CBT-ED), Maudsley Model of Anorexia Nervosa Treatment for Adults or Specialist Supportive Clinical Management (SSCM) (36). These therapies have been evaluated in large-scale trials, which have revealed little or no difference in efficacy between them[4,83-86]. All of these therapies lead to considerable improvements in body weight and reductions in AN symptoms[4]. CBT-ED is the most widely used manualized individual psychotherapy for adult patients, with enhanced CBT for EDs (CBT-E) as described by Fairburn probably being the most widely disseminated CBT-ED for AN[87].

Family based treatment or individual psychotherapy for adolescents?

The most common age of onset of EDs is in adolescence and young adulthood, but the clinical services for adolescents and adults are separate in some countries[4]. This means that patients and their families are often obliged to change treatments when the adolescent patient is transferred to adult services[61]. The choice of treatment should be related to the needs of the patients and their families. For adolescents, FBT is the current leading empirically supported intervention for AN[4,62]. NICE has recently recommended the use of CBT-ED in children and young people when family therapy is unacceptable, contraindicated or ineffective[62]. This recommendation was supported by promising results demonstrated by the application of CBT-E adapted for adolescents with EDs[72]. A recent systematic review found that outpatient CBT-E was well accepted by adolescent patients with AN; it was completed by about two-thirds of participants and produced improvements in eating-disorder psychopathology and general psychopathology, and remission from AN was achieved by about 50% of patients at the 12-mo follow-up[88].

Some of the differences and similarities of FBT *vs* individual psychotherapy were discussed in a recent conceptual comparison of FBT and CBT-E[72]. Briefly, parental involvement in FBT is vitally important for the ultimate success of the treatment. In CBT-E, parental involvement is useful but not essential[72], with their role being simply to support the implementation of the one-to-one treatment. Both types of treatment address adolescent development, but in FBT the adolescent is not viewed as being in control of his/her behavior (*i.e.* the ED is considered to be controlling the adolescent). This is corrected in the first phase of the treatment by improving the parental control over eating[72]. In CBT-E, the adolescent is helped to learn how to control his/her behavior, and parents may help and support the adolescent in taking control[72]. In FBT, the adolescent is initially not actively involved and plays a more passive role, although their role becomes more active in the second and third phases of the treatment, while in CBT-E the adolescent is encouraged from the beginning to become actively involved in the treatment[72]. CBT-E for adolescents does not use directives or coercive procedures. The patients are never asked to work on issues that they do not consider to be a problem, as that would tend to increase their resistance to change. The key strategy of CBT-E is to create a formulation of the main mechanisms maintaining their individual eating problems, and actively involve the patient in the decision to address them, including their low weight. If they do not reach the conclusion that they have a problem to address, the treatment cannot begin or must be suspended.

A lack of insight and motivation for change in the young person is one of the main reasons why FBT is often preferred by both healthcare services and parents. However, most adolescents are able to reach the conclusion that they have a problem to address if they are introduced to CBT-E by a trained psychotherapist[61,72,89]. Once the patient is engaged in the process of change, their personal eating-disorder

psychopathology (outlined in the formulation) is addressed *via* a flexible series of sequential cognitive behavioral procedures and strategies, integrated with progressive patient education[61]. Despite several differences, the general strategy that is common to FBT and CBT-E is to address the maintaining mechanism of the eating-disorder psychopathology, especially undereating, as opposed to exploring any potential causes of the eating-disorder psychopathology. Both treatments take an agnostic view of the cause of the illness; that is, no assumptions are made about the potential origins of EDs[72].

Evidence-based treatment

Some clinical services still do not provide patients with evidence-based psychological treatments, or else they rely on therapists who deviate from the established protocols. The dissemination of FBT, CBT-E and other evidence-based treatments needs to be promoted. Web-centered training programs designed to enable simultaneous training of large numbers of therapists in different countries is a potential solution[61].

Severe and extreme anorexia nervosa

In DSM-5, severe AN is defined as AN with a BMI of 15.00-15.99 kg/m^2, while extreme AN is defined as a BMI < 15.00 kg/m^2 (see Table 1)[2]. Most of the studies on outpatient treatment of AN have included patients with mild or moderate AN. However, some studies have shown that outpatient treatment can be a valid alternative to inpatient treatment in cases of severe or extreme AN if the patient is medically stable[83,90,91]. Outpatient treatment must be safe, otherwise concerns regarding the medical risks will become the focus, rendering psychotherapy difficult or impossible to perform. When a patient is medically stable there is no significant risk of dangerous complications during therapy. These issues are discussed in more detail below in the section on medical management and in the treatment section.

In a case series of 30 patients aged ≥ 17 years with a mean BMI of 15.1 kg/m^2 (range 12.82-15.99) at baseline, 66% completed outpatient CBT-E and demonstrated both considerable weight gain and reduced psychopathology at the end of treatment[90]. Among the 20 patients who completed the treatment, 11 (55%) were classified as having a "full response", corresponding to BMI ≥ 18.5 kg/m^2 combined with a global score on the Eating Disorder Examination Questionnaire (EDE-Q) of less than 1 SD above the community mean[87]. Moreover, among the 9 patients with BMI < 18.5 kg/m^2, 7 (35%) had a BMI that was classified as being of mild severity (≥ 17.0 kg/m^2 according to the DSM-5) and 2 (10%) had a BMI of moderate severity (16.00-16.99 kg/m^2), while no patient was classified as having severe or extreme AN. Changes remained stable at the 1-year follow-up, and no severe complications were observed in the study[90]. These findings indicate that outpatient CBT-E is a valid alternative to inpatient treatment for severe and extreme AN when the patient is medically stable.

SE-AN

A substantial subgroup of patients with AN develop SE-AN[92]. This is currently a rather ill-defined patient population. SE-AN is characterized by: (1) A persistent state of dietary restriction, underweight and overvaluation of weight/shape with functional impairment; (2) Duration longer than 3 years; and (3) Exposure to at least two appropriately delivered evidence-based treatments[41,93]. It is difficult to define what an appropriate treatment is, and a duration of longer than 3 years is very common among patients with AN. In addition, the criteria for recovery from AN remain unclear, so this population is potentially very large. In a 22-year follow-up study of 246 patients with AN and bulimia nervosa, the patients were assessed at 9 years and at 22-25 years after inclusion. Approximately half of those with AN who had not recovered by 9 years progressed to recovery by the 22-year follow-up[94]. These findings argue against the implementation of palliative care for individuals with SE-AN. At present only one formal RCT has been published on the treatment of patients with SE-AN. In that study, 63 patients with an AN duration of at least 7 years were randomized to receive either CBT or SSCM, both adapted for the treatment of SE-AN and both in an outpatient setting. A very low attrition rate was observed, and small effects on the BMI and quality of life were detected in both treatment groups[95]. Raykos *et al*[96] compared illness severity and duration with outcome among 134 patients with SE-AN who received CBT-E in an outpatient setting and found that the illness severity and duration had no effect on outcome. In an inpatient study by Calugi and colleagues, 66 adult patients were divided into groups according to their illness duration: ≤ 7 or > 7 years. All patients received inpatient intensive CBT-E as described by Dalle Grave[97], and the two groups showed similar improvements in BMI and eating-disorder symptoms at the end of treatment and at the 12-mo follow-up[98]. Thus, there appears to be either a weak or no association between AN duration and the effect of treatment among patients with SE-AN[99]. Although the findings of several studies indicate that these patients can benefit from psychotherapy, many with SE-AN are not provided with a treatment program when they seek care[41]. Their presence in an eating-disorder unit can exert complicated effects on the milieu, with a significant proportion of SE-AN patients reporting having experienced coercive efforts to increase their body weight[41]. The poor understanding and paucity of treatments for SE-AN has been described as a crisis in the field of EDs[41].

Hypophosphataemia

During the first weeks of refeeding the patient's blood levels of phosphate may drop significantly with an increased risk of cardiac arrhythmia. If not treated promptly in a patient with severe or extreme AN, critical hypophosphatemia may quickly ensue, which can lead to cardiac arrythmia, refeeding syndrome with heart failure, respiratory failure and central nervous system symptoms[50,100]. The clinical interview should include efforts to detect the risk of a sudden intake of large amounts of food, as part of binge-eating/purging AN. The BMI at the start of treatment and the food intake during the preceding 10 d indicate risk of significant hypophosphatemia during the first weeks of refeeding[101, 102]. Gradual increase of food intake during the first weeks of treatment significantly decreases the risk of significant hypophosphatemia. The AN-related inhibition of food intake will usually cause slow increase in the food intake in outpatient treatment. Mild hypophosphatemia can be treated with oral supplements, while significant hypophosphatemia is treated with intravenous phosphate. Patients with AN and a significant risk of severe hypophosphatemia should be treated as inpatient during the first weeks of refeeding.

Hypokalemia

Loss of potassium is usually caused by vomiting or other purging, but significant hypokalemia may also be seen as part of a refeeding reaction caused by increased insulin release induced by food intake. The insulin induces an intracellular flux of potassium with concomitant hypokalemia. Hypokalemia is associated with risk of cardiac arrythmia. Potassium intake the last hours before blood sampling may result in falsely increased potassium readings. Moderate hypokalemia is treated with oral supplements, while severe hypokalemia is treated with intravenous infusion. Patients with recurrent hypokalemia would usually not be regarded as sufficiently stable for outpatient therapy, partly because refeeding can exacerbate the condition[103].

Alkalosis

In purging, gastric acids are lost and alkalosis may be the consequence. Venous base excess can provide valuable information about alkalosis due to purging. As acid-base disturbances tend to develop before hypokalemia, venous base measurements may be more sensitive to purging than are blood levels of potassium. Alkalosis usually resolves rapidly when purging has stopped and the patient is rehydrated [103].

Hypoglycemia

Significant hypoglycemia is a common problem in AN, both for the restricting and binge-eating/purging subtypes. The main symptoms are dizziness or feeling of weakness, sometimes related to physical activity or after consuming sugar-containing nutritious drinks. If sugar is absorbed quickly it may induce hyperglycemia with concomitant insulin release and hypoglycemia[104]. Severe hypoglycemia is associated with an increased risk of arrythmia. Hypoglycemia usually resolves with refeeding and is not usually a problem when normal weight is re-established. Symptomatic hypoglycemia in patients with severe or extreme AN is usually not compatible with safe outpatient psychotherapy[34,105].

Hyponatremia

Isolated moderate hyponatremia is usually of little or no clinical importance, but severe hyponatremia warrants more detailed assessment and careful inpatient treatment[106].

Decreased glomerular filtration rate

The glomerular filtration rate may decline over time[1,107]. Impaired renal function is frequently overlooked by physicians. Clinicians should consider collecting 24-h urine and calculate creatinine clearance to correctly assess renal function in patients with SE-AN[108].

Low blood counts and anemia

Blood count often reveals leucopenia, granulocytopenia and mild thrombocytopenia. These low blood counts are usually moderate, have no clinical significance and typically resolve with refeeding. In rare cases extreme granulocytopenia or extreme thrombocytopenia indicate the need for inpatient care to manage risk of infection or bleeding[109,110]. Moderate anemia is common. It may be normocytic or macrocytic, even though vitamin B12 and folate may be normal[34]. Sometimes iron supplement is necessary, but the condition typically resolves with refeeding.

Vitamin deficiencies

Several vitamin deficiencies are common in AN. Specifically, deficiencies in fat-soluble vitamins such as vitamin D are common[111]. Routine supplementation with age-appropriate oral multi-vitamin and multi-mineral supplement is recommended[62]. Usually, vitamin D and calcium would be included in these supplements.

Patients with a low intake of bread or other grain products may be at risk of developing thiamine deficiency. Severe thiamine deficiency can be fatal. Patients with suspected thiamine deficiency should be advised to take oral supplements or injections[112,113].

Mineral deficiencies

Magnesium deficiency in AN is usually related to reduced intake, but laxatives and diuretics may also cause magnesium deficiency[102]. Deficiency may cause fatigue, muscle cramps, mental problems, cardiac arrythmia and osteoporosis[114]. Mild or suspected deficiency is treated with oral supplements [102]. Deficiency in zinc may cause depressive symptoms, reduced height growth and lack of appetite. Patients with low intakes of fish and meat should take an oral multi-mineral supplement containing zinc[115].

Elevated liver enzymes

Elevated aminotransferases are common in patients with AN. A mild increase in aminotransferases during the initial weeks of refeeding should not cause alarm or slow down the rate of refeeding[116]. While the liver enzyme values in AN can reach severe levels, a supervised increase in food intake and return to a healthy body weight usually rapidly leads to normalization of elevated aminotransferases caused by starvation and refeeding[116].

Electrocardiogram alterations

Sinus bradycardia, which is sometimes associated with orthostatic hypotension, is often observed in patients with severe or extreme AN[34]. An electrocardiogram (ECG) with corrected QT (QTc) interval measurement is usually performed to assess risk of arrythmia. When detected, a prolonged QTc interval is usually a consequence of QT- usage of interval-prolonging medications or electrolyte disturbances [117]. Most ECG abnormalities respond to adjustment of medication and electrolytes and most do not need further investigation[4].

Generally, if the clinical and biochemical assessment suggests a significant risk of arrythmia, inpatient assessment and medical stabilization is necessary before refeeding is commenced.

Osteoporosis

This serious complication affects up to 50% of patients with AN and can be associated with a life-long elevated fracture risk and the debility that ensues with spinal vertebral compression fractures, among other conditions[118]. Measuring bone mineral density is indicated if the patient has had AN for more than 1 year or amenorrhea for more than 9 or 12 mo[34]. Bone densitometry should be conducted every 2 years during the active phase of AN[34]. Bone mineral density is usually expressed as the T-score, which compares the measured score with that of healthy young adults.

Patients with AN and a T-score of -1.5 to -2.5 (osteopenia) should be advised to focus on weight restoration, and adequate vitamin D and calcium intake[119]. A T-score of less than -2.5 indicates that the patient has osteoporosis. In addition to weight restoration with resumption of normal menses, supplementation with calcium, vitamin D or bisphosphonates is often considered. Only a few studies support the utility of bisphosphonates in AN, but their usage seems to reduce the risk of future spine and hip fractures[119]. However, there are significant safety concerns regarding the use of bisphosphonates, including fetal malformation in pregnant females who are exposed to them[119]. Some studies support the use of transdermal estrogen therapy in patients with AN and osteoporosis. Several RCTs have demonstrated that oral contraceptives are not effective in the treatment of osteoporosis in patients with AN[119].

Inpatient treatment

Patients who have an ED that cannot be managed safely in the outpatient setting or do not respond sufficiently to outpatient treatment are usually advised to enter hospital as a day patient or receive residential or inpatient care. Two main groups of patients are usually transferred to inpatient care: (1) Those who need inpatient psychotherapy in order to gain weight or to stabilize purging[97]; and (2) those who are unable to benefit from inpatient psychotherapy but are in need of supportive care, usually due to medical complications or suicide risk. Some guidelines also recommend inpatient treatment in cases with a BMI of < 15 kg/m^2[1,120]. However, BMI alone may be of limited value as a criterion for inpatient care[83,90,91].

Various inpatient treatments for children and adolescents have been developed. In one study a family-based inpatient program was used to treat 57 patients during the period 2008-2014, and 37 patients consented to take part in a follow-up study[121]. The average length of hospital stay was 20.6 ± 13.6 wk. The average time between discharge and follow-up was 4.5 ± 1.8 years. A total of 65% of the participants had achieved a normal body weight (BMI ≥ 18.5 kg/m^2) and were classified as "weight recovered" at follow-up. These findings indicate that adolescents who are unable to benefit sufficiently from FBT in the outpatient setting may benefit from a family-based inpatient program.

If outpatient treatment of an adolescent or an adult has revealed stable engagement in therapy, but the patient has been unable to obtain sufficient weight gain, inpatient intensive treatment should be considered. For example, a patient who starts outpatient CBT-E for AN but is unable to achieve sufficient weight gain can enter inpatient intensive CBT-E[122,123]. These programs usually last 13 wk. During inpatient treatment, CBT-E is used to help the patient to address their psychological maintaining mechanisms while normal weight is re-established. Transfer to day-patient care or directly to outpatient CBT-E enables the patient to meet everyday challenges without returning to eating-disorder behaviors [122]. According to a recent review intensive CBT-E for the inpatient treatment of adolescents with AN was particularly effective, with approximately 80% of patients achieving normal weight by the 12 mo follow-up[88]. These studies suggest that outcome could be improved if outpatient and inpatient treatments are applying similar psychotherapeutical methods.

Indications for hospitalization for supportive care are usually risk of arrythmia, profound hypotension or dehydration, severe electrolyte abnormalities or risk of suicide. In intensely ill patients who are unable to benefit from outpatient or inpatient psychotherapy a multidisciplinary treatment team could be the best alternative. Treatment is designed by the different team members in regular meetings. The influence of specialists of pediatrics, internal medicine or intensive care medicine can be adapted to the need of the patient[50].

The available findings on inpatient treatment of AN, which mainly come from observational cohort studies, indicate that in a large percentage of patients inpatient treatment is associated with weight restoration and improvements in eating-disorder psychopathology. But unfortunately many patients experience relapse after discharge[61,124]. Studies have indicated that 30%-50% of patients need to be rehospitalized in the first years following discharge[125].

Relapse prevention

Relapse prevention forms part of most psychotherapies, both inpatient and outpatient treatments. But relapse after the end of treatment remains a significant challenge. The usual strategy adopted for addressing relapse after inpatient treatment has been to provide some type of post-hospitalization treatment. Preliminary evidence, which remains to be validated, suggests that CBT is beneficial for patients with AN[61,126] as relapse prevention. One large trial tested Internet-based CBT added to TAU *vs* TAU alone in the post-hospitalization treatment phase in 258 females[127]. CBT completers had greater improvements in BMI compared with those who received TAU only. These findings indicate that the relapse-prevention effect of CBT can be delivered *via* the Internet.

MEDICAL MANAGEMENT

The medical complications of AN affect all organs and systems, and are generally due to weight loss, malnutrition and purging behaviors[106,128].

Purging

Most patients with AN have the restricting subtype, but a significant proportion has binge-eating/purging AN with self-induced vomiting or the misuse of laxatives, diuretics or enemas (see Table 1). A study of laxative use among adolescents with AN found a prevalence of 12%[129]**.** Taking high doses of laxatives is associated with electrolyte disturbances, dehydration and secondary hyperaldosteronism, which can be most challenging during therapy due to the accumulation of water with significant weight gain and oedema[103]. This is usually addressed during psychotherapy[87]. In order to avoid sudden fluid retention with unacceptable weight gain, laxatives should be gradually decreased over a period of 1-2 wk. During the last week, the patient should start taking stool softeners such as lactulose to reduce the tendency for constipation[103]. If the patient is taking extreme doses of laxatives and has very high blood levels of aldosterone, inpatient treatment during the laxative discontinuation may be indicated. However, laxative discontinuation is usually achieved in the outpatient setting[87]. Vomiting is addressed as part of outpatient psychotherapy[87]. Due to loss of acid and potassium, acid-base disturbances and hypokalemia may occur. Hypokalemia is associated with significant risk of cardiac arrhythmia. Severe hypokalemia is an emergency and is treated with inpatient intravenous infusion of potassium[60].

Excessive exercise

Varying degrees of excessive exercise are common in AN. A French study[130] found that more than half (54%) of eating-disorder patients exercised for at least 6 h/wk. However, only a small minority of patients (5%) reported vigorous, compulsive exercise for at least 6 h/wk[18,130]. Excessive exercise is associated with increased risk of fractures[131]. Excessive exercise is sometimes used to compensate for specific episodes of perceived or actual overeating and can be regarded as being related to purging. However, a significant number of patients report that exercise is mainly used to regulate mood[132]. As it is a maintaining factor of the ED, excessive exercise is addressed in the psychotherapy[87].

Outpatient medical management

Most of the medical complications associated with AN can be resolved to a normal status with weight restoration and nutritional rehabilitation. However, some complications can be fatal if not diagnosed and treated adequately and some other complications may persist and cause reduced quality of life (growth retardation, osteoporosis and renal insufficiency). The medical evaluation is aiming at detecting comorbidity and complications. As part of the comorbidity assessment and differential diagnostic considerations tests to detect coeliac disease (*e.g.*, transglutaminase antibodies), thyroid disease (blood levels of thyroxin and thyroid stimulating hormone) and prolactinoma (blood prolactin) are usually performed.

Many patients with AN experience pain in different parts of the body. Pain in the back can be related to minor fractures in the spinal column, which are usually compression fractures. Fractures induced by minimal trauma can significantly impair the quality of life. Attacks of chest pain could indicate pneumothorax or rib fractures, which sometimes occur with minimal trauma.

Gastrointestinal (GI) complaints are especially frequent in AN, with more than 90% of patients reporting GI complaints including postprandial fullness, early satiety, abdominal distention, pain, nausea and obstipation[50,133-135]. These symptoms sometimes increase after food intake and may inhibit attempts to eat sufficiently. Potential reasons for these problems other than AN should be assessed before initiating therapy. If no specific gastrointestinal disorder is diagnosed the symptoms may be regarded as secondary to the ED. Management of the symptoms should be discussed with the patient as part of the psychotherapy[134,136].

There is an increased risk of sudden cardiac death related to malnutrition in AN[50]. Assessment of the risk of sudden cardiac death is essential when determining which patients should receive inpatient medical stabilization prior to commencement of outpatient treatment. This evaluation requires detailed medical, psychiatric, and nutritional assessments, a physical examination, and laboratory testing as described in the treatment section.

A comprehensive account of medical management is outside the scope of this review but is available in the Management of Really Sick Patients with Anorexia Nervosa (MARSIPAN)[60] and Junior MARSIPAN guideline[137]. The scientific background for basic risk assessment and medical management of the most important medical complications relevant for outpatient treatment are discussed in the clinical interview and the physical assessment section and in the treatment section.

ETHICAL ISSUES

A small proportion of patients do not appreciate the severity of their illness, even when they are in a life-threatening situation, which may interfere with their ability to make decisions about life-saving treatment[4]. In countries where compulsory care is possible, an important ethical dilemma may emerge: how many times should compulsory care be provided, and for how long should it be continued?

Those who have been in compulsory care several times sometimes need multidisciplinary treatment to survive their exacerbations. The costs for the patients, their families and the healthcare providers are significant, and sometimes patients or their healthcare providers want to discuss the possibility of ending multidisciplinary healthcare. This would raise several ethical questions. What is the prognosis if multidisciplinary treatment is continued and what quality of life can be expected? This ethical problem is growing with our increasing knowledge around how to assess medical risks and manage life-threatening complications. Patients with life-threatening AN can survive for several decades if they are brought to healthcare centers before they are at a terminal stage with irreversible life-threatening complications. The 22-year follow-up study of Eddy and colleagues found that a significant subpopulation of the patients who had not recovered by 9 years had recovered by 22 years[94]. There are insufficient data to enable a conclusion to be drawn on the probability of recovery after 20 years of SE-AN. In addition, patients with SE-AN can improve their quality of life by weight gain[138,139].

The stakeholders involved when a process towards ending treatment commences need to be determined. Yager[140] suggested that different stakeholders should be involved, including the patients and their families, healthcare providers (the entire treatment team as well as the institutional administrators and their boards), payers and policymakers. There is also a need to determine who is going to make a decision and at what level such decisions should be made[140,141]. Our poor understanding of SE-AN and the paucity of available treatments AN makes this ethical issue even more complicated[41].

EMERGING THERAPIES AND OUTSTANDING RESEARCH ISSUES

AN as a metabo-psychiatric disorder

The Psychiatric Genomic Consortium was established in 2007 to conduct meta- and mega-analyses of genome-wide genomic data related to psychiatric disorders. The Eating Disorders Workgroup has been

a part of this consortium since 2013. Members of this workgroup have performed genome-wide association studies, which have revealed strong associations between AN and insulin sensitivity, low BMI-adjusted fasting serum insulin and several other metabolic markers[30]. The increase in insulin sensitivity was greater than what could be explained by low BMI. The authors of that report suggested that it is time for a reconceptualization of AN and that it should be regarded as a metabo-psychiatric disorder[30,142].

Several other studies support the reconceptualization of AN towards regarding it as a metabo-psychiatric disorder. Our brain and gut are linked through humoral and bidirectional neural connections that allow fast and complex interactions *via* the brain-gut axis[143]. Several studies indicate that decreased food intake may alter the normal interactions in the brain-gut axis, thereby enhancing the maintenance of AN[142]. GI hormones and gut microbiota may be essential participants in the regulation of the brain gut axis. Several GI hormones are released by food intake and may participate in the development of the maintaining mechanisms in AN[144]. Some of them have been shown to induce anxiety and panic attacks in animals and humans when administered in supraphysiological doses, and in susceptible patients[145-147]. Ghrelin is a peptide hormone synthesized in the enteroendocrine cells of the stomach. It is released by calorie restriction and stress to stimulate appetite and increase food intake. Food intake increases ghrelin levels in healthy individuals, whereas in AN patients it is followed by decreased levels of ghrelin. Clinical trials of the novel ghrelin receptor agonist RM-131 in the treatment of AN are currently being performed[148].

Microbiota in AN

The gut microbiota influences the extraction of energy from food and body weight gain, as well as appetite, gut permeability, inflammation and complex psychological behaviors such as depression or anxiety, all of which may play roles in the development and maintenance of AN. Nutrition is one of the main factors that influence the gut microbiota. Starvation has a substantial impact on the gut microbiota [149], inducing cell death in several fast-growing bacteria, while allowing the proliferation of slowly growing bacteria and bacteria that are able to feed on indigestible fiber or the mucin layer along the gut wall. Thus, food restriction might exert its maintaining effects on AN by affecting the gut microbiota [150,151].

The malnutrition-related alterations in the gut content also induce several metabolic effects, partly mediated by short-chain fatty acids (SCFAs) produced by the gut bacteria[152]. The pathways of SCFA production are relatively well understood, with major products being acetate, propionate and butyrate [153]. Acetate production pathways are widely distributed among bacterial groups, whereas pathways for the production of propionate and butyrate appear more highly conserved and substrate-specific. It has been proposed that an elevated colonic production of SCFA could stimulate numerous hormonal and neural signals at different tissue sites that would cumulatively suppress the energy intake[154]. There is emerging evidence that the anorexigenic hormone peptide YY (PYY) plays a role in the pathogenesis of AN[155]. PYY is produced mainly in the colon, where SCFAs are produced at high levels through the fermentation of fiber by the gut microbiota[156]. SCFAs strongly stimulate the production of PYY in human enteroendocrine L-cells in the gut wall[152].

Microbiota-modulating strategies may be promising determinants of the healing process and the outcome of AN[149]. Nutritional interventions, including supplements that have the potential to influence the gut microbiota, are important research targets when developing future AN therapies, especially for patients who are unable to normalize their gut microbiota by a sufficient food intake during psychotherapy. Fecal microbiota transplantation (FMT) has been associated with significant improvement in diseases such as irritable bowel syndrome[157,158]. FMT involves transplanting the entire fecal microenvironment, including SCFAs and other substances with potential effects on food intake and brain-gut interactions[159]. The first case reports on FMT in patients with SE-AN found weight gain in one patient, but no effect on BMI in another[160,161]. Data from the ongoing pilot study "Fecal Microbiota Transplantation (FMT) in the treatment of SE-AN"[162] may provide valuable information on feasibility of FMT in patients with SE-AN. Future studies should clarify whether interventions aimed at establishing normal brain-gut interactions can reduce dropout and relapse rates among patients with AN. Tools to assess and describe the responses mediated through the brain-gut axis, including clinical, biochemical and radiological methods like functional magnetic resonance imaging[163], should be further developed. Such approaches would allow interactions between the brain and gut in AN and the possibility of treatment with brain-gut modulation to be assessed.

Other emerging therapies

Other emerging therapies focus on direct effects on the brain in regulating food intake and the cognitive alterations related to AN. Transcranial direct-current stimulation is a method for directly modulating the excitability of cortical regions using small electrical currents. A pilot study that applied this method to the left dorsolateral prefrontal cortex in seven patients with AN found that the procedure was well tolerated, and was associated with modest short-term improvements in scores on eating scales in five of the patients[148]. Another non-invasive technique, repetitive transcranial magnetic stimulation, was investigated in ten patients with AN, which revealed that a single session of repetitive transcranial magnetic stimulation was well tolerated and improved feelings of fullness and anxiety[148].

Deep brain stimulation is another neuromodulatory technique that is currently under investigation for the treatment of AN[148]. It is a surgical procedure that involves the implantation of stimulating electrodes into key brain structures that are believed to drive the pathological activity associated with AN[148]. One study applied continuous stimulation of the subcallosal cingulate for 1 year to 16 patients with SE-AN, which increased BMI from 13.8 to 17.3 kg/m^2[164]. However, these findings in studies of neuromodulatory techniques might be driven by a placebo effect as well as an increased motivation of patients to engage in TAU[4,165,166].

Learning models suggest that exposure-like therapy could be effective in AN. Exposure interventions to AN-related stimuli (*e.g.*, food, body) have been tested in small trials of patients with AN[4,167,168]. Virtual-reality environments have also been used to manage food-related or body-related fears in small trials including patients with AN[4,169].

Current research activity in the field of EDs is inadequate given the cost of the problem, since 8- to 10-times more research funding is provided for depression and psychosis[4]. Several projects have aimed at producing research priorities for AN. The Canadian Eating Disorder Priority Partnership was established to identify and prioritize the ten top research priorities for females aged at least 15 years with AN, by incorporating equal input from those with lived experience, families, and healthcare professionals. Their conclusions were published 2020[170]. The top priorities identified were related to "treatment gaps" and the need for "more surveillance data". Furthermore, a panel consisting of Australian members of the Australian and New Zealand Academy for Eating Disorders and the National Collaboration for Eating Disorders in Australia[171] were invited to take part in a survey on how important it was that each of 29 research areas received funding. The 291 responders were eating-disorder specialists, consumers/carers or affiliates (clinicians and researchers not specializing in EDs, along with participants from the industry). The top-three-ranked priorities for research funding were "accessible evidence-based treatments", "origins of EDs" and "early detection and intervention". Within these domains, the following research areas all received very high ratings: "early intervention at all critical risk periods", "what to do when first line treatments don't work", "enhancing existing eating-disorder treatments", "accessible services" and "early detection"[171].

These surveys support research on "early detection and intervention", including those that aim to decrease the time from the onset of AN to the initiation of evidence-based treatment.

Studies on the transition to adult psychiatric services ("treatment gaps") will be valuable, including those designed to determine how to ensure that the patient accepts transfer to another therapist, who will sometimes apply a different treatment approach. Comparisons of different models of organization including studies on the co-localization of adolescent and adult treatment services could be part of this research. Long term effects of outpatient *vs* inpatient therapy should be assessed. If a substantially larger proportion of the patients may be treated as outpatients, the problems related to coordinating outpatient and inpatient therapy can be reduced.

Studies on the effects of implementing treatment standards and therapist training suitable for therapists in decentralized treatment units may inform decisions around how to make services for early intervention more accessible.

National quality-assurance registries for EDs are being established in several countries[172], which can provide surveillance data and detect possible regional inequalities in healthcare. Studies on early intervention with optimally implemented, effective evidence-based methods would be of great value. How non-completion rates can be decreased is another essential research question to address ("enhancing existing eating-disorder treatments"). Establishing standards for practice and training appears to be of value for standardizing care and enhancing existing eating-disorder treatments[173].

In line with the aim of "enhancing existing ED treatments", several adaptations to FBT have been published in order to enhance effectiveness[174]. Still, outstanding dilemmas need research attention. Especially, FBT places a heavy task on parents, and it may be impossible for some families to mobilize for a variety of reasons, *e.g.*, other mental illnesses. Mental health services need guidance on how to support these families so the young person can stay home and yet receive the necessary day-by-day support. This is especially crucial in cases where the young person does not have the motivation and/or ability to initiate behavioral change that is needed to succeed in CBT-ED.

In light of the moderate success rates across all psychotherapeutic treatment for AN, two types of research might improve outcomes. First, information is needed on what works for whom, in order to choose more personalized modes of treatment. Second, research on how to maximize the effect of non-specific factors in therapy, *e.g.*, therapeutic alliance, may provide avenues for better outcomes in the future. One example of a service development that aims to adapt specific aspects of treatment to individual needs is the "PEACE pathway" which targets individuals with AN and autism spectrum disorders[175].

Turning to the medical management of AN, the mechanisms underlying sudden death in these patients warrant further research, since data are lacking regarding the cardiac rhythm at the end of life. The most significant other knowledge gaps include the management of bone mineral density, and the GI problems in AN, as well as electrolyte regulation, mechanisms of kidney damage and refeeding syndrome[176].

Despite the significant progress that has been made in the understanding of the medical complications of AN, considerable work remains to be done. There are both research and treatment gaps, and bridging them will ultimately improve the medical treatment outcomes of patients suffering from AN [176].

Defining the diagnostic criteria is probably the most important first step in SE-AN research. In addition, the criteria for recovery from AN will help delineate the population and help to define the aims of healthcare for SE-AN. Progress in understanding how to manage the medical complications of this illness has provided the potential to significantly increase the quality of life and life expectancy in this patient population. Some of the emerging strategies might improve the results of psychotherapy, including treatment aiming at reducing attrition, relapse and thereby decreasing recruitment to the SE-AN population. Early intervention with evidence-based therapy including engagement of the large population of patients with SE-AN who is not seeking healthcare will perhaps be the most important prophylactic intervention to reduce the number of patients with SE-AN.

CONCLUSION

Outcome of AN is unacceptably poor. However, the last decades have brought several effective psychotherapies for children, adolescents and adults. For many reasons, outpatient treatment is preferable. Inpatient treatment is needed in cases of acute medical risk, severe suicidal risk and when weight gain is not obtained in outpatient treatment in spite of engagement in therapy. Due to progress in understanding of the medical complications of AN more patients can safely be treated as outpatients. The implementation of effective psychotherapies and safe outpatient medical management are valuable tools for improvement of healthcare in AN.

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Effects of antiseizure medications on alternative psychosis and strategies for their application

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Abstract

Forced normalization (FN) is a unique phenomenon that is often seen in the treatment of epilepsy. FN is characterized by abnormal mental behavior and disordered emotions in epilepsy patients despite a significantly improved electroencephalogram and successful seizure control; the occurrence of FN seriously affects patients' quality of life. The causes of FN include antiseizure medications (ASMs), epilepsy surgery and vagus nerve stimulation, with ASMs being the most common cause. However, with the timely reduction or discontinuation of ASMs and the use of antipsychotic drugs, the overall prognosis is good. Here, we perform an extensive review of the literature pertaining to FN, including its epidemiology, possible mechanisms, clinical features, treatment and prognosis.

Key Words: Forced normalization; Antiseizure medications; Neurotransmitter; Antipsychotic drugs; Electroshock

Core Tip: Forced normalization (FN) is often seen in the treatment of epilepsy. FN is characterized by abnormal behavior and disordered emotions in epilepsy patients despite a significantly improved electroencephalogram and successful seizure control; the occurrence of FN seriously affects patients' quality of life. However, with timely recognition and treatment, the overall prognosis is good.

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INTRODUCTION

Alternative psychosis is also known as forced normalization (FN). This phenomenon is characterized by abnormal mental behavior and disordered emotions after the seizures of active epilepsy patients are controlled and their electroencephalograms (EEGs) have significantly improved. FN is unique to the pharmacotherapy of epilepsy and often leads to the failure of epilepsy treatment. Although FN is still an entity with uncertain pathophysiology, it has received extensive clinical attention in recent years, and significant progress has been made regarding its pathogenesis and treatment strategies[1-5]. Recently, Calle-López *et al*[5] conducted a study on 193 FN episodes and found that the causes included antiseizure medications (ASMs), epilepsy surgery and vagus nerve stimulation (VNS), with ASMs being the most common cause. This article aims to describe the clinical features and possible mechanisms of FN induced by ASMs and to explore strategies for its treatment.

HISTORICAL EVOLUTION OF FN

FN was first described by Landolt[6] in the 1950s. They noticed that after active epilepsy was well controlled and the EEG signals returned more or less to normal, the patients developed episodic behavioral abnormalities and mood disorders. They could not reasonably explain this clinical phenomenon and thought it might be a unique phenomenon in epilepsy patients. In 1965, De Jorio *et al*[7] summarized the clinical manifestations of this "Landolt FN". At the same time, Tellenbach[8] published a study on the electrophysiological characteristics of Landolt FN and began to explore its possible mechanism; since then, this unique phenomenon in the treatment of epilepsy has received more extensive attention.

The first discovery regarding the cause of FN was the influence of a type of herbal ingredient. Later, with the widespread use of ethosuximide (ESM) in clinical practice, it was found that the number of patients with FN gradually increased[9]. In 2005, Clemens[10] reported that FN could be caused by lamotrigine (LTG). There were also reports of FN caused by valproic acid (VPA), phenytoin (PHT), and zonisamide (ZNS)[4,5,9]. In recent years, studies on the relationships between FN and ASMs have focused more on levetiracetam (LEV)[11,12]. In 2018, Esang *et al*[12] systematically discussed the clinical features and treatment strategies for FN and explored its relationship with ASMs, which made the clinical diagnosis and treatment of FN more rational.

EPIDEMIOLOGICAL CHARACTERISTICS OF FN

Carazo Barrios *et al*[3] found that 10 patients met the criteria for FN in a cohort analysis of 4468 patients with epilepsy; Wolf *et al*[13] reported that the prevalence of FN in epilepsy patients was 7.8%. Calle-López *et al*[5] used the MEDLINE, Embase, Cochrane and Scielo databases to collect clinical data, electrophysiological characteristics and imaging data of patients with FN for a systematic analysis. They found that 48.5% of cases of FN were caused by ASMs, 31.8% by epileptic surgery, and 13.6% by VNS.

PATHOGENESIS OF FN

The pathogenesis of FN is unclear and lacks a solid experimental basis. It is difficult to establish a suitable animal model. Therefore, the current understanding and various hypotheses regarding the mechanism of FN are mainly based on the observation of responses to three clinical treatments: Epilepsy surgery, VNS and ASMs[3,9,14-17].

Human behavioral changes associated with FN are related to the midbrain limbic system, which has a wide range of connections with the cortex. After surgical removal of brain tissue from patients with epilepsy, the epileptic seizures stopped, but FN occurred, which indicated that the mental behavior abnormalities associated with FN have an anatomical basis[9]. On this basis, Wolf[18] proposed that the formation of FN may be the result of epileptic discharges that are not fully suppressed and spread along specific channels under the cortex after epileptic seizures are controlled, but the specific location is not clear.

Although the surgical methods and excision sites of patients undergoing epilepsy surgery are different, they can all develop FN, indicating that its anatomical basis is likely very extensive, and electrical ignition can activate these neuronal activities. The most obvious feature of FN is that when epileptic seizures are effectively controlled, abnormal mental behavior and emotional disorders appear. Electroshock can not only relieve the mental symptoms of patients with FN but also cause the occurrence of epilepsy, so it has effects on these mutually antagonistic outcomes, which indicates that it may participate in the formation of FN. After VNS, FN will occur with the reduction or cessation of seizures, which supports the hypothesis that electric ignition participates in the formation of FN and

plays an important role in FN[3,9,19].

FN caused by ASMs is related to "pharmacological kindling". It has long been known that certain drugs that selectively activate the limbic system can cause behavioral abnormalities, which are similar to the electrical activation of the limbic system; accordingly, this drug-induced activation is called pharmacological kindling. Many drugs can cause epilepsy, which supports the existence of pharmacological kindling. Existing studies have found that electrical kindling can effectively induce seizures, but pharmacological kindling can result in behavioral changes[9].

Pharmacological kindling is related to neurotransmitters. Brigo *et al*[20] reported on two patients with tuberous sclerosis with FN who had used VPA, LTG, rufinamide, carbamazepine (CBZ), topiramate (TPM), ZNS, and LEV. It has been found that all the drugs that can cause FN can affect the transmitter glutamate. Subsequent research found that drugs that can induce FN, such as TPM, ZNS, and LEV, can affect α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated excitatory synaptic transmission, and drugs that enhance AMPA-mediated glutamatergic transmission can treat psychosis, which indicates that impaired glutamatergic neurotransmission may be related to FN. Additionally, researchers have found that repeated administration of small doses of dopamine agonists and stimulants will produce increased behavioral responses, while dopamine antagonists can cause seizures while producing antipsychotic effects. The mechanism of electroshock treatment of psychosis is also related to upregulating dopamine and its metabolites, which suggests that dopamine may play an important role in mediating FN, and the hypothesis of "dopamine igniting" has been proposed[9].

CLINICAL FEATURES OF FN

The main clinical manifestations of FN are that patients with active epilepsy have abnormal mental behavior and mood disorders after the seizures are controlled, and most patients have improved or normal EEG synchronization[2-4]. Recently, Calle-López *et al*[5] analyzed 193 FN episodes reported in the literature and found that 69.4% of patients presented with mental disorders; 27.9%, mood disorders; and 10%, dissociation. The clinical features of FN are summarized in Table 1.

FN induced by different ASMs

LEV: LEV is the ASM that most often causes FN, but whether FN occurs during LEV use is related to many factors.

Age of onset: FN induced by LEV, as currently reported in the literature, mostly occurred in patients between 9-56 years old. Kawakami *et al*[21] reported that a 9-year-old girl with idiopathic epilepsy had seizures and EEG results that gradually worsened after taking VPA and benzodiazepines and then was switched to LEV. The epileptic seizures stopped, and the epileptiform discharges on EEG disappeared, but the patient showed anger and violent behavior. The authors suggested that this was FN induced by LEV. Kikuchi *et al*[22] reported a 10-year-old girl with unclassified epileptic encephalopathy, and FN occurred after taking LEV. Topkan *et al*[11] reported that the age of the patient with FN after taking LEV was 56 years old.

Gender: FN often occurs in women. The Calle-López *et al*[5] review on FN found that 60% were women. Of the 10 patients reported by Carazo Barrios *et al*[3], 6 were women. At present, it has been reported in the literature that FN induced by LEV has occurred in females, with the exception of one male[3,11,19-22].

Time of onset: The onset time of FN is not certain. Topkan *et al*[11] reported that a 56-year-old woman was treated with LEV for epileptic seizures. Forty-five days after the seizures ceased, the patient had a personality change accompanied by visual hallucinations. The 24-h EEG examination was also normal. This author believes that this was FN induced by LEV. Kikuchi *et al*[22] reported a patient with epileptic encephalopathy. One day after taking LEV, his tonic and myoclonic seizures as well as the paroxysmal discharge on the EEG disappeared, but there was a slow response and dyskinesia. After the recurrence of myoclonic epilepsy, his psychiatric symptoms also disappeared. This author believes that this was FN caused by the administration of LEV. Green *et al*[19] reported a 14-year-old boy who had a history of mental illness. One month after treatment with olanzapine, he developed tonic-clonic epileptic seizures. LEV was used to prevent the seizures. After 6 mo, he developed FN manifesting as self-harming cutting behavior and auditory and visual hallucinations.

Main clinical manifestations: FN induced by LEV mainly manifests as abnormal mental behavior and dissociative personality. Topkan *et al*[11] reported that a 56-year-old patient had obvious personality changes after the seizures stopped that were accompanied by visual hallucinations and déjà vu, and the mental symptoms disappeared after treatment with quetiapine. Kawakami *et al*[21] reported that after the use of LEV in a patient with epilepsy, the epileptic seizures stopped, but FN occurred. The patient showed episodic anger and violent behavior. The simultaneous EEG examination revealed that the epileptiform discharge had disappeared. Green *et al*[19] reported a 27-year-old female patient with spastic cerebral palsy and febrile convulsions. At the age of 22, she was diagnosed with epilepsy, and treatment with LEV was initiated. Subsequently, FN occurred with many behavioral abnormalities, such as decreased alertness and concentration, confusion, delusions, and auditory and visual hallucinations.

Table 1 Clinical features and treatment of forced normalization

Classification			Ref.
Clinical features	LEV	Abnormal mental behavior and dissociative personality	[11,19,21]
	ESM	Mania; visual and olfactory hallucinations; paranoid psychosis	[9,24,25]
	VPA	Paranoid thoughts, agitation, sleep disturbances, confusion	[26,27]
	LTG	Irritable, inattention, insomnia, paranoid thoughts, and hallucinations appearing	[3,10]
	LCM	Paranoid behavior and psychotic symptoms	[3,28,29]
	TPM	Abnormal mental behavior	[20]
	ZNS	Communication disorders, interpersonal tension and stereotyped behaviors	[20,30]
	VGB	Hallucinations and anxiety	[1,31]
	PHT	Paranoia, restlessness, aggressiveness, command hallucinations, and stereotyped, short-term psychomotor excitement and impulsive violent events, irritability	[3,12,32]
	ESL	Behavioral disturbances, psychosis	[3]
	BRV	Dysthymia, generalized anxiety disorder	[3]
Treatment	Dose reduction or drug withdrawal		[3-5,10,11,15,21]
	Control of mental symptoms (haloperidol, risperidone)		[2,3,5,25,26,33]
	Electroshock		[19]

LEV: Levetiracetam; ESM: Ethosuximide; VPA: Valproate; LTG: Lamotrigine; LCM: Lacosamide; TPM: Topiramate; ZNS: Zonisamide; VGB: Vigabatrin; PHT: Phenytoin; ESL: Eslicarbazepine; BRV: Brivaracetam.

The symptoms continued to worsen until the seizures reappeared; the psychiatric symptoms then began to improve, and the aggressive behavior decreased.

Possible mechanism of the FN induced by LEV: Helmstaedter *et al*[23] conducted genetic polymorphism analysis on 290 patients with mental symptoms taking LEV and found that patients who had dopaminergic genetic variants were prone to irritation and aggressive behavior after taking LEV, suggesting that it may be related to FN. This author believes that the use of pharmacogenomics methods to examine the side effects related to mental behavior may provide a useful tool for the prediction of poor mental outcomes related to ASMs.

ESM: ESM is the main ASM for the treatment of epileptic absence seizures and certain epileptic syndromes. It was also the first drug found to cause FN[9]. Recently, Yamamoto *et al*[24] reported an 11-year-old boy with intractable myoclonic epilepsy and severe psychomotor development delay treated with ESM. After his myoclonic seizures were fully controlled, he had episodic behavior changes (mainly mania), and the EEG examination at this time was almost completely normal. This author believes that this was FN caused by ESM. Apap Mangion *et al*[25] reported a man with drug-resistant epilepsy featuring both focal and generalized seizures. After ESM treatment was started, the seizures stopped, and the EEG was normal; however, 3 wk into the use of this medication, FN occurred and manifested as visual and olfactory hallucinations that rapidly deteriorated into paranoid psychosis. After ESM treatment was stopped and olanzapine was added for one month, his psychiatric symptoms disappeared; he then restarted taking a small dose of ESM without the recurrence of psychiatric symptoms.

VPA: VPA is another of the main drugs causing FN. Banwari *et al*[26] reported a case of an epilepsy patient who had a disease course of 13 years and had not been treated with ASMs. One week after the start of treatment with VPA, the patient's seizures stopped, but FN occurred. With low-dose risperidone treatment, the patient's mental symptoms disappeared. Turan *et al*[27] reported that a patient with epilepsy developed mental symptoms under combined treatment with VPA and LTG. This author believes that there are related underlying mechanisms among ASMs, seizure control and psychosis development.

LTG: Two of the 10 patients reported by Carazo Barrios *et al*[3] were patients with FN induced by LTG. Both of them were male; one of them was 41 years old at the time of FN, and another was 40 years old. The former had focal epilepsy, and the latter had generalized seizures. Clemens *et al*[10] also reported 2 patients with FN induced by LTG. One patient was a 10-year-old girl with normal development and no history of neuropsychiatric disease. At the age of 7 years, paroxysmal and transient clonic movements of

the right arm and hand occurred. She was diagnosed with epilepsy when she was 8 years old, and treatment with CBZ was ineffective. After switching to LTG, the epileptic seizures stopped, the epileptiform discharge of the interictal EEG disappeared, but mental and behavioral disorders appeared. After reducing the daily dose of LTG, the mental symptoms gradually disappeared. Another patient was a 43-year-old woman with temporal epilepsy, complicated partial seizures appeared from the age of 6 years, and treatment with CBZ was ineffective; CBZ was replaced with LTG, and the dose was gradually increased to 100 mg bid. After a few days, the seizures disappeared, but the patient became increasingly irritable with inattention and insomnia and finally paranoid thoughts and hallucinations appearing. At the same time, EEG showed that all paroxysmal activities had completely disappeared, and the diagnosis was FN. The dose of LTG was gradually reduced to 50 mg bid, and the mental symptoms disappeared after haloperidol treatment.

Lacosamide: Lacosamide (LCM) is a new ASM in clinical use in recent years. It is mainly used for the adjuvant treatment of partial seizures. It has a good safety profile with the most common side effects, including dizziness, headache, diplopia, nausea, nasopharyngitis and vomiting. In 2013, Chatzistefanidis *et al*[28] reported that young female patients with drug-resistant partial epilepsy developed FN after treatment with LCM. In 2015, Pinkhasov *et al*[29] reported that after using LCM, a young woman experienced psychiatric symptoms. This author believes that this is the first case report of FN induced by LCM in the United States. Carazo Barrios *et al*[3] reported three patients with FN related to LCM administration. Among them, one patient was a 44-year-old woman with focal seizures caused by cortical dysplasia, and FN occurred after taking LCM. Another patient was a 42-year-old woman with unknown disease etiology and developmental delay, presenting focal or focal secondary generalized seizures. The seizures disappeared after taking LCM, but behavioral abnormalities appeared. The other patient was a 66-year-old man with focal epilepsy caused by meningoencephalitis, and FN occurred after the use of LCM. This author believes that this was FN induced by LCM.

TPM: TPM is another ASM that can cause FN. Brigo *et al*[20] reported a 33-year-old female patient with tuberous sclerosis. The initial treatment with VPA, LTG, and rufinamide was ineffective. After switching to TPM, the patient's seizures stopped, and the epileptiform discharges on the 60-min EEG were reduced by more than 50%, but severe abnormal mental behavior appeared. These mental abnormalities disappeared after stopping the drug, and the patient developed mental abnormalities again after adding TPM. This author believes that this was FN caused by TPM.

ZNS: Hirose *et al*[30] reported a 5-year-old child with refractory epilepsy. After receiving ZNS treatment, the seizures stopped, but FN appeared, manifesting as communication disorders, interpersonal tension and stereotyped behaviors. This situation persisted after ZNS was stopped, and seizures then reappeared. This author believes that although most of the patients with FN are adults and adolescents, ZNS can induce mental disorders even in young children. Brigo *et al*[20] reported a 33-year-old female patient with vascular encephalopathy following cerebral bleeding due to moyamoya disease who had seizures, and VPA treatment was ineffective. After switching to ZNS, the epileptic seizures stopped, but the patient showed obvious mental and behavioral abnormalities. This author believes that this is consistent with a diagnosis of FN and that these contradictory outcomes with treatment are extremely challenging.

Vigabatrin: Vigabatrin (VGB) has also been reported to cause FN. Weber *et al*[31] reported that a young patient had symptomatic and refractory focal seizures due to middle cerebral artery obstruction. After five weeks of treatment with VGB, the seizures stopped, but obvious abnormal mental behavior appeared after two weeks. This author believes that this was FN caused by VGB. To date, there have been more than 13 patients with FN caused by VGB[1].

PHT: Hirashima *et al*[32] reported an 11-year-old girl with FN of occipital epilepsy. This patient had no family history of epilepsy or mental disorders and developed normally. At the age of 11, she developed a fever-free generalized tonic-clonic seizure and was diagnosed with epilepsy. After PHT (37.5 mg bid) was administered, the seizures were controlled. Three days later, she developed mental symptoms, paranoia, restlessness, aggressiveness, command hallucinations (command voices from strangers) and stereotyped, short-term psychomotor excitement and impulsive violent events; recurring, neurological examinations were normal, clinical chemistry and clinical hematology test values were within the normal range, and brain magnetic resonance imaging scanning and analysis also found no abnormalities. After stopping PHT, her mental condition did not improve. Based on the patient's clinical course, this author believes that she developed FN by taking PHT. Esang *et al*[12] reported a 26-year-old female patient with no history of mental illness. Her family members described that she had been diagnosed with epilepsy in 2016 and received LEV treatment, which was initially effective; however, she had frequent seizures 1 year later, and then PHT (0.1 g tid) was added. The epileptic seizures stopped, the EEG and the head CT scan were normal, but FN occurred. There were severe mental abnormalities, severe agitation, irritability, and "all day anger", and the patient was finally hospitalized for impulsive behavior. Carazo Barrios *et al*[3] also reported one patient with FN caused by PHT among 10 FN patients.

Others: Among the 10 patients reported by Carazo Barrios *et al*[3], FN was also caused by eslicarbazepine and brivaracetam.

TREATMENT

De Toffol *et al*[4] advocated that the treatment of FN should be divided into two steps. First, it should be assessed whether the current ASM treatment is reasonable. Second, the appropriate antipsychotic should be selected. The reduction or withdrawal of suspicious ASMs and the addition of antipsychotic drugs are the main management methods of FN. The treatment of FN is summarized in Table 1.

Dose reduction or drug withdrawal

In most cases, the reduction in the dose of the drug inducing FN or the withdrawal of the suspicious drug can effectively alleviate the clinical manifestations of FN. Among the 10 FN patients reported by Carazo Barrios *et al*[3], one patient stopped suspicious ASMs and started using antidepressants, and another patient reduced the dose of suspected ASMs, which relieved the symptoms. Topkan *et al*[11] reported that patients who took LEV had FN, and the symptoms disappeared after switching to PHT. Of the 193 FN episodes studied by Calle-López *et al*[5], 47% of the patients ceased using the suspected ASMs, 25% received a dose reduction, and 28% maintained use of the original drug. In 87% of patients who withdrew their medication, FN was completely in remission, compared with 75% of those who did not discontinue. However, the treatment recommendations across different drugs are not exactly the same. It is necessary for patients receiving LEV to stop the drug when FN occurs. The symptoms of FN caused by LTG will improve by dose reduction[3,10,15,21].

Control of mental symptoms

The mental symptoms of patients with FN are often severe, which affects the quality of life of these patients. In severe cases, it may cause self-injury or other forms of injury, which requires antipsychotic treatment. Carazo Barrios *et al*[3] reported that 5 of 10 FN patients received antipsychotics or increased their antipsychotic doses, and 5 patients started taking antidepressants or increased their antidepressant drug doses. The symptoms of FN were subsequently relieved. In an analysis of 193 FN episodes, Calle-López *et al*[5] found that 73% of patients received antipsychotic treatment; haloperidol (35.4%) was used the most often, followed by risperidone (18.7%). These studies are supported by studies by Banwari *et al*[26] and Apap Mangion *et al*[25]. They also reported that the use of risperidone relieved the symptoms of FN patients. Domzał[33] suggested that haloperidol is a suitable treatment method. Agrawal *et al*[2] advocated a first choice of second-generation antipsychotic drugs, especially risperidone, because there is little interaction between this drug and other drugs, and the risk of side effects is also low.

However, whether antipsychotic treatment is provided does not affect the overall prognosis of patients. The complete remission rate of patients who received antipsychotic treatment was 56.2%, while the complete remission rate of those who did not receive antipsychotics was 92.8%. The reason is not clear[5].

Others

Not all patients with FN can be treated by discontinuing or reducing the dose of suspicious drugs and adding antipsychotic drugs. For those who are unresponsive to drug treatment, Green *et al*[19] suggested that electroshock treatment can be considered; they reported that two patients with FN were treated with electroshock methods and achieved good results. Therefore, they suggested that this method may be a reasonable treatment for FN. Kikuchi *et al*[22] reported a patient with epileptic encephalopathy who developed FN after taking LEV. They did not change the original drug, and the patient subsequently experienced epilepsy; the original mental symptoms completely disappeared.

PROGNOSIS

The overall prognosis for patients with FN induced by ASMs is good. Seven out of 10 patients reported by Carazo Barrios[3] had a good prognosis, with seizures not reappearing after the FN symptoms disappeared, and only 3 patients had a poor prognosis with recurrent attacks. Among the 193 episodes of FN studied by Calle-López *et al*[5], 65% of patients had complete control of their psychiatric symptoms, 27% had mild psychiatric symptoms, and 6% of patients had long-term symptoms. Among them, symptoms in women were more likely to be relieved than those in men, and children (< 14 years) were more likely to experience relief of their symptoms than adults. Seventy-five percent of patients with focal epilepsy experienced complete relief, and 61% of patients with generalized seizures experienced complete relief.

CONCLUSION

In conclusion, FN is a unique and easily overlooked entity. When ASMs such as LEV, ESM, LTG, and VPA are used to control epileptic seizures, if abnormal mental behavior occurs despite successful seizure control and normal EEG results, the possibility of FN should be considered. FN often leads to failure of the treatment of epilepsy and affects the quality of life of the patient. However, if this phenomenon is detected in time and corresponding measures are taken, such as dose reduction or withdrawal of the causative drug and administration of antipsychotic drugs, the overall prognosis is good. Exploring the factors related to FN caused by different ASMs can further improve clinicians' understanding of FN. The specific pathogenesis of FN needs further research in the future.

FOOTNOTES

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MINIREVIEWS

Role of serendipity in the discovery of classical antidepressant drugs: Applying operational criteria and patterns of discovery

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Abstract

The role played by serendipity in the origin of modern psychopharmacology has proven to be controversial in scientific literature. In its original meaning (Walpole), serendipity refers to discoveries made through a combination of accidents and sagacity. We have implemented an operational definition of serendipity based on finding something unexpected or unintended, regardless of the systematic process that led to the accidental observation, and we have established four different patterns of serendipitous attributability. In this paper, we have analyzed the role of serendipity in the discovery and development of classical antidepressant drugs, tricyclic antidepressants and monoamine oxidase inhibitors as well as heterocyclic, "atypical" or "second generation" antidepressants. The discovery of the antidepressant properties of imipramine and iproniazid, the prototypes of tricyclic antidepressants and monoamine oxidase inhibitors, respectively, fits the mixed type II pattern; initial serendipitous discoveries (imipramine was an antipsychotic and iproniazid was an antituberculosis agent) led secondarily to non-serendipitous discoveries. But the other

components of these two families of drugs were developed specifically as antidepressants, modifying the chemical structure of the series leaders, thereby allowing all of them to be included in the type IV pattern, characterized by the complete absence of serendipity. Among the heterocyclic drugs, mianserin (originally developed as an antihistamine) also falls into the type II pattern.

Key Words: Serendipity; Antidepressants; Imipramine; Iproniazid; Psychopharmacology; History of neurosciences

Core Tip: In this paper, we have analyzed, for the first time, the role of serendipity in the discovery and development of classical antidepressant drugs through our operational definition of serendipity. We have assigned each of the classic antidepressants its corresponding pattern of serendipitous attributability according to four different patterns.

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INTRODUCTION

The era of modern psychopharmacology began in the late 1940s, with the publication of the antimanic effects of lithium by Australian psychiatrist Cade[1]. However, it was in the 1950s that what has come to be known as the "psychopharmacological revolution"[2] came into being, with the introduction of the large families of pharmacological agents that are still in use today: typical neuroleptics or antipsychotics, benzodiazepine anxiolytics and the two large groups of classic antidepressants, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)[3]. All of these psychotropic drugs drastically changed the state of psychiatric care, starting from a fundamentally empirical therapeutic approach, which nevertheless allowed for a gradual understanding of some of the neurobiological bases of mental illnesses and how to treat them.

The year 1957 should be regarded as a key date in modern psychiatry, as this was the year when the first two specific antidepressant drugs in history were introduced into clinical practice, belonging to two completely different pharmacological families and two completely different geographical areas of research. Iproniazid, an MAOI agent, was the result of a research process developed in the United States, and imipramine, the prototypical representative of the TCA family, was developed and studied in Europe[4]. Prior to the clinical introduction of these antidepressant agents, the therapeutic tools used to manage affective disorders were extremely limited[5]. At the beginning of the 20th century, chloral hydrate, barbiturates, amphetamines and opiate derivatives were used in agitated melancholic patients. During the first half of the century, excluding biological treatments (insulin comas, chemical, electrical shock therapies, and "sleep cures"), there were only a few nonspecific chemical preparations available to doctors, such as dinitrile succinate, malonic nitrite and lactic acid, all of which had rather unsatisfactory antidepressant results[6,7] confirmed in the few clinical studies carried out. However, this was also due in part to Freudian ideas prevalent until the 1950s that depressive syndromes had only psychodynamic, not biological, causes, meaning that these patients could not benefit from treatment with pharmacological agents[8,9].

In the specific field of antidepressant drugs, TCA agents that ushered in a new era in the treatment of depression are still the benchmarks today, especially in clinical research, and have the same efficacy rates as other antidepressants that have appeared since then. However, unlike TCAs, which continue to be used in clinical practice though not as a first-line treatment, the use of MAOIs has largely fallen off, due primarily to their adverse effects and problems of interactions with other psychostimulant drugs and tyramine-rich foods, which can lead to tragic hypertensive crises. However, atypical depressions are still candidates for treatment with these drugs. During the 1970s, new heterocyclic antidepressants appeared, known at the time as "atypical" or "second generation" antidepressants (maprotiline, mianserin, trazodone, viloxazine, nomifensine). The main characteristic of which was that they were more selective in their action on monoaminergic transmission systems. All of these drugs can be categorized as traditional antidepressants (Table 1).

Table 1 Classification of classical monoaminergic antidepressants according to action mechanism and historical perspective on their clinical introduction

Family	Mechanisms of action	Acronym	Prototype substance	Period
Tricyclic antidepressants	5-HT and NA reuptake inhibitors with blocking action of diverse receptors	TCA	Imipramine	1957-1980
Monoamine oxidase inhibitors	Irreversible MAO inhibitors	MAOI	Phenelzine	1958-1965
Heterocyclic or "second generation" antidepressants	NA reuptake inhibitors with blocking action of diverse receptors		Maprotiline	1967-1980
	Antagonists of α_2 auto-receptors		Mianserin	1970-1980
	DA and NA reuptake inhibitors		Nomifensine	1970-1980
	5-HT reuptake inhibitor and antagonist of 5-HT_2 receptors		Trazodone	1970-1980

5-HT: Serotonin; NA: Norepinephrine; DA: Dopamine; TCAs: Tricyclic antidepressants; MAOIs: Monoamine oxidase inhibitors.

Finally, in the late 1980s, a new series of drug families were introduced into clinical practice, including selective serotonin reuptake inhibitors, which were widely used and accepted. These drugs offered considerable advantages over their predecessors, particularly in terms of safety and tolerability, and opened up the field of antidepressant therapy to non-psychiatrists. The first selective serotonin reuptake inhibitor was zimelidine, which was withdrawn from the market, but we can say that the period of "modern" antidepressants began with the successful clinical introduction of fluoxetine[10].

Serendipity may have played a crucial role in the process of discovering classic psychotropic drugs during the 1950s[11,12], although opinions in scientific literature in recent decades are rather contradictory possibly due to a lack of consensus on what is meant by serendipity. In the specific field of science, this concept has traditionally been associated with those discoveries or findings of a fortunate and unexpected nature, fortuitous events or accidental encounters ("happy accident," "pleasant surprise," *etc.*), although its meaning has also been linked to the very concept of chance, randomness or coincidence.

The differences in opinion about the role of serendipity or chance discoveries in science may lie in the semantic ambiguity of the term "serendipity." The origin of which can be traced to correspondence between the English writer, politician and historian Horace Walpole, 4th Earl of Oxford and the British diplomat Sir Horace Mann. One epistle in this fluid correspondence, which refers to the classic Persian tale *The Three Princes of Serendip*, contains the two components that should make up the concept of serendipity: accidents and sagacity[13]. Therefore, it is sagacity that marks the difference between serendipitous discovery and the absence of discovery in the presence of relevant accidental information. But is not sagacity a basic and indispensable component of the scientific mentality itself? If the answer is yes, this element must be present irrespective of whether the phenomena observed in the scientific discovery were foreseen or not. However, we have postulated that there is a structural difference in this approach. Sagacity always precedes and leads observation in non-serendipitous discoveries, but in serendipitous discoveries, sagacity manifests itself after the unexpected observation has been made. However, even this assessment leads to interpretative problems as once scientists have made their discovery, they tend to explain them as a consequence of perfectly planned working hypotheses even when they take place in a completely random way.

Thus, from a conceptual point of view, we can conclude that serendipitous discovery is the discovery of something unsought, regardless of the systematic process that led to the accidental observation. Viewed in this light, serendipity is undoubtedly a key factor in the creative process in the arts and humanities[14,15]. However, it can also be seen as an integral part of the development of social sciences and of course of biomedical sciences in general and psychopharmacology in particular.

Kubinyi[16] briefly analyzed the discoveries of different pharmacological agents in which serendipity was somehow involved, and Hargrave-Thomas *et al*[17] confirmed that 24% of all commercially available drugs were positively influenced by serendipity during their development, particularly psychopharmaceuticals. In this sense, the discovery of most of the psychopharmacological agents that revolutionized the care of mental illnesses during the 1950s has not escaped this conceptualization either[13]. However, although the researchers responsible for these discoveries have themselves reported that chance was a key factor in their findings, the role of serendipity in the early days of psychopharmacology is still far from being established.

To address this point further, we have established an operational definition of serendipity based on four different patterns of attributability[13,18], which allows us to reflect on the actual role that serendipity played in the findings that shaped the origins of modern psychopharmacology. In this paper following this approach, we will look at the role played by serendipity in the discovery of the classic antidepressant drugs.

PATTERNS OF SERENDIPITOUS ATTRIBUTABILITY

In previous papers[13,18], we have proposed a standardized definition for the term serendipity in the field of science, given the semantic ambiguity of this concept. This "operational" definition would establish that serendipity is the discovery of something not sought. Moreover, we have proposed a working definition of serendipity[13,18] based on four different patterns of serendipitous imputation in the drug discovery process (Figure 1): (1) The first pattern, which would encompass pure serendipitous discoveries, was more frequent in the first half of the 20th century; (2) The second pattern, which is a variant of the previous one, would correspond to those initial serendipitous discoveries that secondarily lead to non-serendipitous discoveries; (3) The third pattern would include non-serendipitous discoveries that are secondarily partnered with serendipitous discoveries; and (4) The fourth pattern of non-serendipitous discoveries, in line with our operational definition of finding something unsought, has become more and more frequent since the second half of the last century. In the latter pattern, beyond serendipity, drugs evolved out of systematic research programs specifically designed to develop effective drugs for different pathological conditions.

Mixed discoveries (patterns 2 and 3) were very common towards the middle of the 20th century (coinciding with the so-called "golden decade" of psychopharmacology in the 1950s) and were characterized by initial serendipitous discoveries (in some cases in laboratory animals) leading secondarily to non-serendipitous discoveries and vice versa.

Prior to applying the attributability criteria, a detailed historical study of the development process of each of the antidepressant drugs analyzed was carried out, using the original articles in which the first pharmacological and clinical data on these drugs were published. This was done using most important databases in this field (Medline, Embase, Scopus), the documentation services of the pharmaceutical companies that have marketed these drugs and the documentation available in the Network for the History of Neuropsychopharmacology, coordinated by Thomas A. Ban (Vanderbilt University), the series of interviews entitled *The Psychopharmacologists*, by David Healy (Arnold-Oxford University Press), the *History of Psychopharmacology* collection of the Collegium Internationale Neuro-Psychopharmacologicum, coordinated by Thomas A. Ban, David Healy and Edward Shorter and edited by Animula and the documentary background on the history of psychopharmacology by Prof. López-Muñoz.

SERENDIPITY IN THE PROCESS OF DISCOVERY OF CLASSICAL ANTIDEPRESSANT DRUGS

Discovery of the antidepressant properties of imipramine and TCAs

The history of the clinical introduction of the first antidepressant drug (from the family of TCA), imipramine, was part of a search for antipsychotic drugs[19,20], following the therapeutic success reported with the clinical introduction of chlorpromazine[21] and reserpine, an alkaloid from *Rauwolfia serpentina*[22] in 1952 (Figure 2). See López-Muñoz *et al*[23-25] for details. These developments intensified the search for substances with similar properties by pharmaceutical companies. Accordingly, the pharmaceutical company J.R. Geigy (Basel) dusted off some phenothiazine substances that it had initially tried to develop unsuccessfully as dyes[8] and later on as antihistamines and hypnotics in the hope that they might have some other psychiatric benefit[8,9,26].

In this context, the Swiss psychiatrist Roland Kuhn, deputy medical director at the Cantonal Psychiatric Clinic in Münsterlingen (near Lake Constance), who had already studied the hypnotic and neuroleptic properties of certain Geigy phenothiazine agents[26,27], asked the Swiss company for new compounds from the phenothiazine family to test them in his psychotic patients. In early 1956, Kuhn received a preparation called G-22355, a substance with the same side chain as chlorpromazine, which had been synthesized by Franz Häfliger and Walter Schindler in 1948 from promethazine by replacing the sulfur bridge of phenothiazine with an ethylene bridge[28]. The substance had been registered in 1951 under United States license number 2554736[29].

Kuhn's extensive clinical research in 1956 soon showed that the agent G-22355 had no appreciable neuroleptic activity. Even patients who had previously been treated with chlorpromazine developed more severe psychotic symptoms not schizophrenic and became clinically disturbed and agitated[30]. However, Kuhn observed that 3 patients diagnosed with depressive psychosis showed a pronounced improvement in their general condition in just a few weeks. The antidepressant effect of this substance, later named imipramine, was therefore completely unexpected and its discovery entirely accidental. In

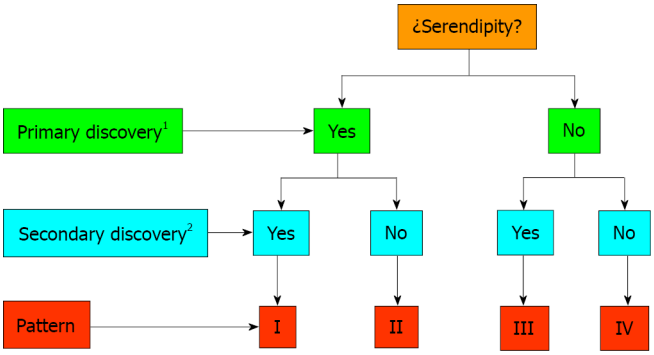

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Figure 1 Diagram of the four patterns of serendipitous attribution in the discovery of pharmacological agents. [1]They usually, but not always, relate to findings in laboratory animals; [2]Findings relating to clinical efficacy.

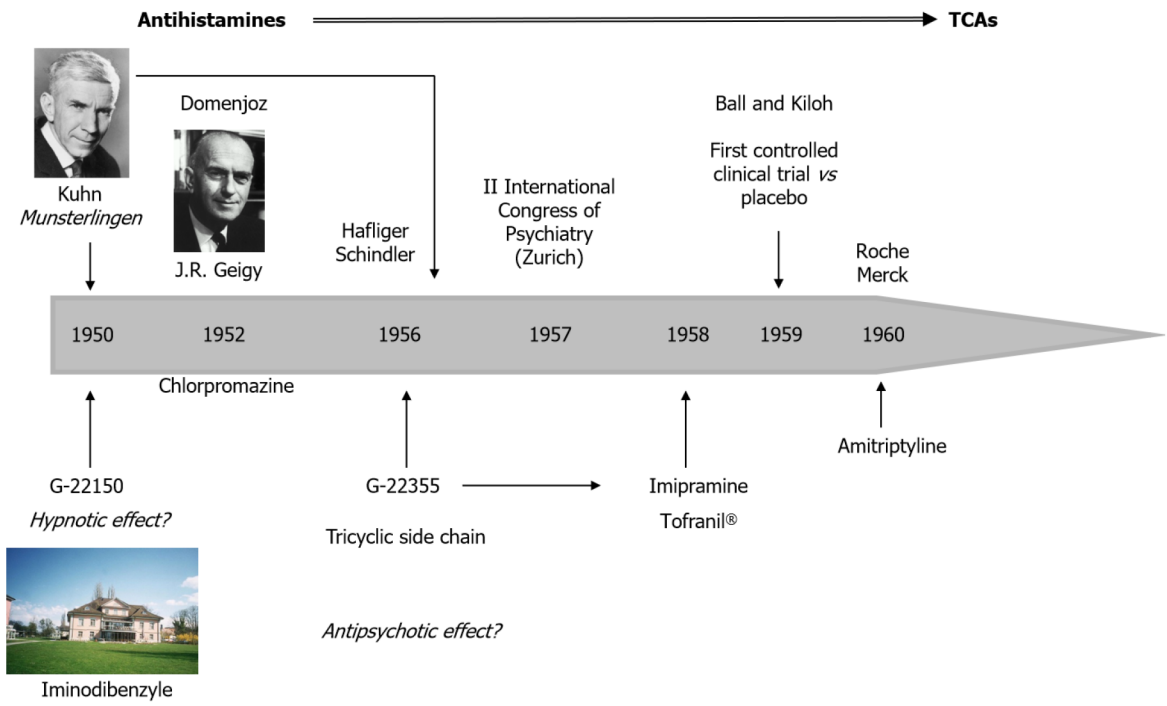

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Figure 2 Historical process of the discovery of tricyclic antidepressants during the 1950s. TCAs: Tricyclic antidepressants.

this regard, the possibility that this substance could have a therapeutic antidepressant effect was first raised by Kuhn in a written communication to Geigy dated February 4, 1956[31].

Subsequently, a further 37 patients with depressive disorders received this drug, demonstrating its particular efficacy in treating depressive disorders[26,32,33]: "The patients appear, in general, more animated, their voices, previously weak and depressed, now sound louder; they are more communicative, the lamentations and sobbing have disappeared. The depression, which had manifested itself through sadness, irritation and a sensation of disaffection, now gave way to friendly, joyous and accessible feelings"[32]. Kuhn presented his results at the 2nd International Congress of Psychiatry in Zurich in September 1957 to an audience of just 12 people, using the data obtained from the clinical follow-up of these 40 depressed patients. The proceedings of the conference were published in the August issue of the *Schwizerische Medizinische Wochenschrift*[32]. However, the following year, Kuhn republished his data (with a larger sample of patients) in the *American Journal of Psychiatry*[33], thereby making his discovery internationally known. In this paper, Kuhn extensively described the pharmacological effects, data on efficacy and the adverse effects of imipramine and provided recommendations for its clinical use, dosage and duration of treatment. In this work, Kuhn stated that "the patients got up in the morning voluntarily, they spoke in louder voices, with greater fluency and their facial expression became more lively. They began to do some individual activities, they once more sought to make contact with other people, they began to train on their own, to participate in games, to become happier,

and to recover their ability to laugh"[33].

Geigy introduced imipramine to the local Swiss market at the end of 1957 under the trade name of Tofranil®. It was subsequently introduced in the rest of the European market in the spring of 1958[8,29] and represented a giant step forward in the treatment of depression, being the first representative of a new family of drugs, known as imipraminic or TCAs.

Kuhn had the sagacity to recognize an antidepressant drug when looking for an antipsychotic drug. Kuhn himself commented: "Chance admittedly had something to do with the discovery of imipramine. Chance was not decisive, however, to this had to be added a measure of intellectual achievement that was able to "invent" something completely new, something hitherto unknown, namely a new disease. Göthe put the sense of the matter in a nutshell when he wrote: 'Discovery needs luck, invention, intellect–neither can do without the other'"[34]. Something similar pointed more than a century ago the great Louis Pasteur: "In the realm of scientific observation, luck is granted only to those who are prepared"[35].

The discovery of the antidepressant properties of imipramine is a representative example of how a serendipitous finding, the observation of schizophrenic patients treated with this drug looking for an antipsychotic effect, leads to a planned and non-serendipitous discovery, *i.e.* the antidepressant effect. Therefore, the antidepressant effect of imipramine would fit into the type II pattern of our serendipitous attributability criteria. This pattern of a mixture of serendipitous and non-serendipitous findings was possibly the most common during the early stages of modern psychopharmacology. But it is precisely this dual quality that has been a major source of controversy in attributing serendipity to psychopharmacological discoveries.

Despite the remarkable success of imipramine, the next TCA, amitriptyline, was not introduced to the market until 1961. This molecule was also investigated as an antipsychotic by the pharmaceutical company Merck and Co. For this, they made modifications in the central ring of the thioxanthene family, and in this way, they got the first compound of the dibenzocycloheptadiene group[36]. Merck commissioned Frank J. Ayd Jr., one of the American pioneers in the study of chlorpromazine, to conduct clinical research on this new compound. But Ayd tried it as an antidepressant, following in the wake of imipramine. Ayd treated 130 patients at Baltimore Square Hospital with amitriptyline and found that the antidepressant effect was similar to that of imipramine. The Food and Drug Administration approved amitriptyline for marketing as an antidepressant on April 7, 1961 and it received the trade name Elavil®. This molecule would retain some of the tranquillizing effects of thioxanthenes, thus displacing imipramine in the treatment of patients with agitated or anxious depression.

The introduction of amitriptyline, the second tricyclic agent, by Merck and Co. increased the confidence in these drugs of both general practitioners and specialists. Thanks to the commercial strength of these two pharmaceutical companies and a marketing agreement between them (the joint marketing of both products, Elavil Merck and Tryptizol Roche worldwide, except in the United States where it was only marketed by Merck), amitriptyline quickly became the most prescribed antidepressant at the time.

Simultaneously, Hoffmann-La Roche and H. Lundbeck and Co. had succeeded in synthesizing amitriptyline by modifying the chemical structure of imipramine accordingly. Although due to the priority of their application, Roche received the European marketing rights under the name Saroten® [37].

The discovery of the antidepressant properties of imipramine and its commercial success led to the development of a number of compounds with similar structures and activities (now called "me-too" compounds) in order to identify specific comparative advantages[38]. This subsequently became quite common practice in the field of pharmacological therapeutics. As a result, a number of TCAs were developed during the 1960s. In 1963, nortriptyline was approved in Britain under the name Allegron®, while in the United States it was approved by the Food and Drug Administration in November 1964, when desipramine (J.R. Geigy), the principal urinary metabolite of imipramine, was also approved; in 1966, trimipramine was introduced in Britain and other European countries under the name Surmontil®. These agents were followed by other TCAs: in 1966 by protriptyline (called Concordin® in Europe and Vivactil® in the United States); in 1967 by iprindole (Prondol®); in 1969 by dothiepin (Prothiaden®), an agent not approved in the United States; doxepin[39], introduced onto the European market by Galenus (Aponal®), a subsidiary of Boehringer, and in the United States by Pfizer (Sinequan®) [40]; and clomipramine (Anafranil®), introduced in Europe in 1970, which was not approved in the United States.

All components of the TCA series were developed specifically as antidepressant agents, following in the wake of imipramine and modifying its chemical structure, so they can all be included in the type IV pattern of our serendipitous attribution criteria, in which neither chance nor sagacity played a part (Table 2).

Discovery of the antidepressant properties of iproniazid and non-selective MAOIs

The origin of the first specific antidepressant drugs, MAOIs, can be traced back to hydrazide antituberculosis agents, which had been used since the early 1950s[5,41] (Figure 3). In 1952, Selikoff *et al*[42] began to study the clinical effects of iproniazid at Sea View Hospital on Staten Island (New York). They observed that compared to isoniazid iproniazid had a greater stimulatory power on the central nervous

Table 2 Attribution of serendipity in the discovery of classical antidepressant drugs

Group/Family	Drug	ATC code	Date of discovery (psychiatric introduction)	Effect/primary properties[1]	Effect/secondary properties[2]	Pattern of discovery
TCAs	Imipramine	N06AA02	1951 (1957)	S	NS	II
	Amitriptyline	N06AA09	1958 (1961)	NS	NS	IV
	Trimipramine	N06AA06	1964 (1966)	NS	NS	IV
	Butriptyline	N06AA15	1964	NS	NS	IV
	Desipramine	N06AA01	1964	NS	NS	IV
	Clomipramine	N06AA04	1963 (1970)	NS	NS	IV
	Nortriptyline	N06AA10	1963 (1967)	NS	NS	IV
	Protriptyline	N06AA11	1967	NS	NS	IV
	Iprindole	N06AA13	1967	NS	NS	IV
	Doxepin	N06AA12	1969	NS	NS	IV
	Dibenzepin	N06AA08	1970	NS	NS	IV
	Maprotiline[3]	N06AA21	1967 (1973)	NS	NS	IV
	Dosulepin	N06AA16	1977	NS	NS	IV
	Amineptine	N06AA19	1978	NS	NS	IV
	Amoxapine	N06AA17	1980	NS	NS	IV
	Quinupramine	N06AA23	1983	NS	NS	IV
	Lofepramine	N06AA07	1989	NS	NS	IV
MAOI	Iproniazid	N06AF05	1952 (1957)	S	NS	II
	Isocarboxazid	N06AF01	1959	NS	NS	IV
	Phenelzine	N06AF03	1960	NS	NS	IV
	Tranylcypromine	N06AF04	1961	NS	NS	IV
	Nialamide	N06AF02	1988	NS	NS	IV
OCA	Trazodone	N06AX05	1966 (1973)	NS	NS	IV
	Nomifensine	N06AX04	1977	NS	NS	IV
	Mianserin	N06AX03	1966 (1979)	S	NS	II

[1]Usually, but not always, correspond to discoveries in laboratory animals.
[2]Discoveries related to clinical efficacy.
[3]Maprotiline is the first tetracyclic antidepressant and is included in the group of "second generation antidepressants." Antidepressant drugs were classified by the Anatomical Therapeutic Chemical classification system controlled by the World Health Organization Collaborating Centre for Drugs Statistics Methodology. This system classifies the active ingredient of a drug into groups according to the organ or system on which they have their effect. https://www.whocc.no/atc_ddd_index/?code=N06AX&showdescription=no.
NS: Non-serendipitous discovery; S: Serendipitous discovery; TCAs: Tricyclic antidepressants; MAOIs: Monoamine oxidase inhibitors; OCA: Other classical antidepressants; ATC: Anatomical Therapeutic Chemical.

system, an effect initially interpreted as a secondary effect of the preparation[42]. The psychological changes observed in tuberculosis patients treated with iproniazid were particularly striking[5,8,43]; these patients showed increased vitality, even a desire to leave the hospital and a gradual increase in social activity. In other types of patients treated with iproniazid, such as patients with rheumatoid arthritis or cancer, similar psychostimulant effects were also observed[44].

But the adverse effects of iproniazid, observed in the first clinical trials with tuberculosis patients, were more frequent than in the case of isoniazid. Therefore, it was abandoned, except for specific cases, such as that of David M. Bosworth, Director of the Department of Orthopedics at St. Luke's and Polyclinic Hospital (New York), who continued to defend the use of iproniazid in bone tuberculosis [45]. But a few astute clinicians saw a "primary effect" in the psycho-stimulant type of "secondary effect" discussed above, which could be useful in other types of patients, mainly of a psychiatric nature. This was the case of Jackson A. Smith (Baylor University, Waco, Texas), who, evaluating the "tranquil-

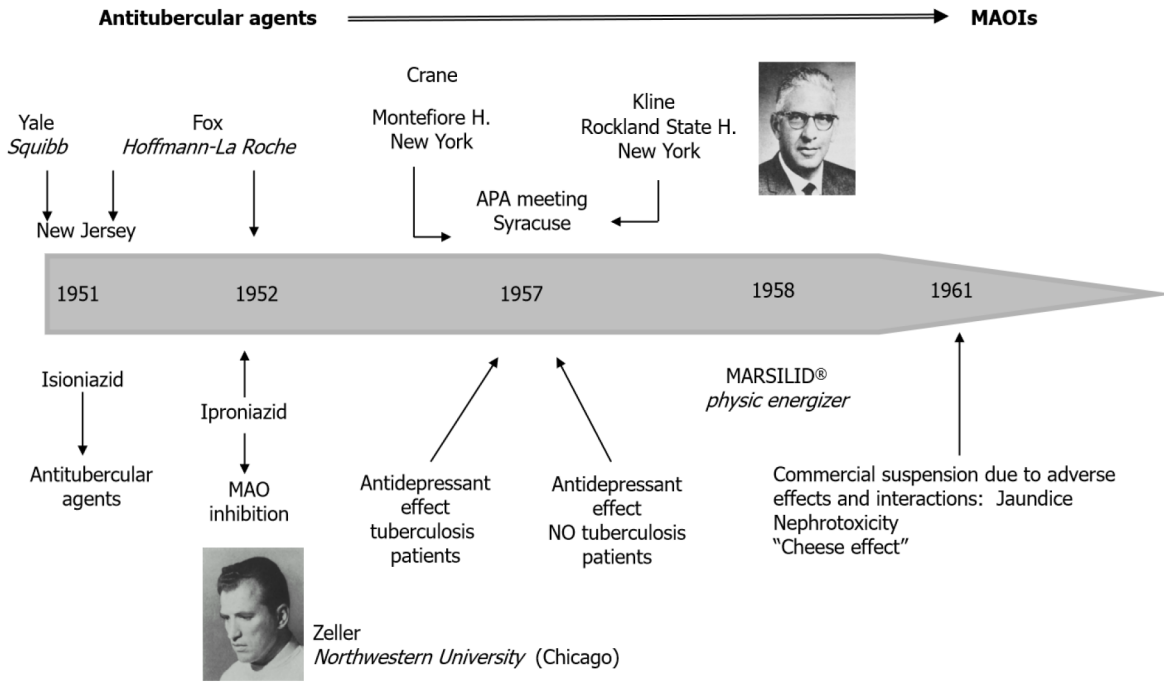

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Figure 3 Historical process of the discovery of monoamine oxidase inhibitors during the 1950s. APA: American Psychiatric Association; MAOI: Monoamine oxidase inhibitors.

lizing" effect of iproniazid observed that of a group of 11 patients treated for 2 wk with this drug, 2 of them experienced a certain improvement (increased appetite, weight gain, increased vitality and improved sleep)[46]. The same was true of Gordon R. Kamman, of the University of Minnesota (Twin Cities)[47] and Carlos Castilla del Pino of the University of Cordoba in Spain, who described the euphoriant and mood-elevating effects of hydrazide therapy in tuberculosis patients[48]. Some studies were even published assessing the mood elevating effect of isoniazid in psychiatric patients[49-51]. In fact, one of these researchers, Max Lurie (Cincinnati), may have coined the term "antidepressant" precisely to describe the effect that this drug had on depressed patients[52].

The year 1957 was fundamental in the history of hydrazide drugs as antidepressants, as the first data on the effects of iproniazid on depression were presented at a meeting of the American Psychiatric Association in Syracuse in April of that year. Although its use was much more limited than isoniazid, George Crane of Montefiore Hospital in New York reported improvement in the mood of 11 out of 20 tuberculosis patients with concomitant depression[53], as did Frank Ayd, an intern at Taylor Manor Hospital in Baltimore[54]. However, these researchers never mentioned iproniazid as an "antidepressant" agent.

Meanwhile, Nathan S. Kline and his colleagues (Harry P. Loomer and John C. Saunders) from Rockland State Hospital (Orangeburg, New York), who were aware of the work of Charles Scott's team at Warner-Lambert Research Laboratories (Morris Plains, New Jersey) particularly the ability of iproniazid to prevent reserpine-induced immobility in mice[55], were the first psychiatrists to assess the efficacy of iproniazid in non-tuberculous depressed patients (chronic psychotic depression). They performed the same procedures on humans as Scott had done on animals. For their study, they recruited 17 severely inhibited patients with schizophrenia and 7 patients with depression from Kline's private practice and gave them a dose of iproniazid 50 mg, 3 times a day. Their results revealed the stimulating effect of iproniazid on depressed patients; 70% of the patients treated with this drug experienced a great improvement, including increased mood, increased appetite and increased interpersonal skills, interest in the environment and in themselves. These same effects were already provided at the Syracuse Meeting, although they were not released until a few years later when they were published[56].

In 1957, Kline[57] published the first neuropsychiatric experiments with iproniazid (previously reported at the American Psychiatric Association Annual Meeting in Syracuse) during a meeting of the Committee on Appropriations of the United States Senate in May[57], proposing the term "physic energizer" to designate the activity of this drug[58]. Two years later, Werner Janzarik proposed at a symposium held in Montreal the use of the term "thymerethics," *i.e.* compounds that act by increasing the stimulatory effects, to refer to all those drugs with effects similar to the new MAOIs.

Although iproniazid was only authorized (with the trade name of Marsilid) for the treatment of tuberculosis patients, its use in depressive patients was massive. Only 1 year after the Syracuse Meeting,

it was estimated that more than 400000 patients with depression were treated with iproniazid[59]. This opened the door to a group of specifically antidepressant drugs, later known as MAOIs, due to the research of Ernst Albert Zeller's team at Northwestern University Medical School (Chicago, Illinois). It was known in 1952 that iproniazid was able to inhibit MAO[60]. Despite all this, iproniazid was withdrawn from the United States market in 1961 following allegations that it induced a number of cases of jaundice and nephrotoxicity.

Serendipity played an important role in the discovery of iproniazid[11]. Thanks to the sagacity of healthcare professionals dedicated to the care of tuberculosis patients, it was realized that certain "secondary effects" of anti-tuberculosis medication of a psychostimulant nature, which appeared by chance, could be useful in psychiatric patients diagnosed with depressive disorders. Therefore, this would fall under a type II pattern under our serendipitous attribution criteria.

Iproniazid soon gave way to other agents with much higher MAO inhibitory potency[61], such as Hoffman-LaRoche's isocarboxazid (Marplan®), marketed in 1959, phenelzine developed by Warner-Lambert (Nardil®)[62], which became available in 1960, and tranylcypromine (Smith, Kline & French) (Parnate®)[63,64], which entered the market in 1961, as well as other hydrazine derivatives (nialamide, mebanazine and pheniprazine) and indole derivatives (etryptamine)[65,66]. The origin of this agent, synthesized in 1948 by Alfred Burger and William L. Yost, is part of the search for new analogues of amphetamines (trans,dl-2 phenylcyclopropylamine sulfate)[67], although its MAOI activity was discovered much later in 1959 by Smith, Kline & French Laboratories[63,68]. Indeed, the fact that tranylcypromine was not a hydrazine derivative aroused some clinical interest, and it was speculated that it could have a better hepatic safety profile than that of other MAOIs known to date[69].

But tranylcypromine was also withdrawn from the United States market in 1964, albeit for other safety reasons, when an increase in the number of drug-related hypertensive crises, some of them linked to intracranial subarachnoid hemorrhages, was reported. It was reintroduced in the same year at the request of specialists and is still in use today. Thanks to the contributions of Barry Blackwell, then a resident consultant in psychiatry at the Maudsley Hospital in London, it was confirmed that these crises were triggered by the concomitant consumption of certain cheeses, given their high tyramine content, hence the term "cheese effect"[70]. The link between the hypertensive crises described by Blackwell and the consumption of tyramine-rich foods is also a clear example of the phenomenon of "serendipity" in psychiatry, according to Blackwell himself[71]. A hospital pharmacist in Nottingham, called G.E.F. Rowe, read an article published by Blackwell[70] in 1963 in *The Lancet* on tranylcypromine and its adverse effects[70] and noted that the symptomatology described was alarmingly similar to that experienced by his own wife when she consumed certain cheeses. These episodes were described in detail in a letter Rowe sent to Blackwell, who was alerted to this dangerous association. Many other foods (yeast products, chicken liver, snails, pickled herring, red wines, some varieties of beer, canned figs, beans, chocolate and cream products, *etc.*) were subsequently found to contain indirectly acting amines (mainly tyramine), which could also cause hypertensive episodes in patients treated with MAOIs.

After the use of iproniazid as an antidepressant, the other agents in this family were incorporated into the antidepressant therapeutic arsenal thanks to recognition of their MAO inhibitory effect, meaning that they would fall into the type IV pattern under our serendipitous attribution criteria, where chance no longer played a role (Table 2).

Heterocyclic or "second-generation" antidepressants

During the 1960s, many changes were made to the dibenzazepine structure of imipramine in order to obtain new antidepressants with superior efficacy and/or an improved adverse effect profile. As a result, the tetracyclic, heterocyclic or "second generation antidepressants"[36], such as maprotiline (Ludiomil®), marketed by Ciba-Geigy in Europe and Japan in 1972[8], mianserin (Tolvon®), nomifensine (Merital®) and trazodone (Desyrel®), were developed. Compared to the classic TCAs, which had a very unspecific mechanism of action [serotonin (5-HT) and norepinephrine reuptake inhibition with blocking action of diverse receptors][72], these drugs had a slightly cleaner pharmacodynamic profile.

The first tetracyclic antidepressant was maprotiline, developed as an antidepressant by Max Wilhelm and Paul Schmidt in 1967 at Ciba. However, the four rings of its chemical structure are not fused together as is the case with other tetracyclic antidepressants. Clinical trials of this agent were also conducted by Kuhn[73]. By contrast, nomifensine is a tetrahydoisoquinoline antidepressant that is not chemically related to TCAs, MAOIs or heterocyclic antidepressants. It is a dopamine and norepinephrine reuptake inhibitor developed as an antidepressant in the 1960s. The pharmacological effects of nomifensine were similar to those of TCAs in animal models of depression but with a much lower rate of sedation[74]. However, it was withdrawn from the market in 1986 due to safety concerns (immune related hemolytic anemia), including some cases of dependence, given its similar mechanism of action to psychoactive drugs such as cocaine.

As far as trazodone is concerned, it is now known to have a dual mechanism of action whereby it inhibits the serotonin transporter and blocks the 5-HT_2 serotonin receptors (both the 5-HT_{2A} and 5-HT_{2C} receptors). But, like TCAs, it also exerts an antagonistic effect on α_1- and α_2-adrenergic receptors and histamine H_1 receptors, with almost no anticholinergic effects[75]. It was discovered in Italy in 1966 at Angelini Research Laboratories by Gorecki and Verbeeck[76] and developed as a second generation

antidepressant following the then current "mental pain" hypothesis, which postulated that clinical depression was associated with a reduced pain threshold[77]. Trazodone was patented and marketed in many countries around the world from 1973 and approved by the Food and Drug Administration as the first non-TCA, non-MAOI antidepressant in 1981. These three compounds can be included in our type IV pattern of attributability as serendipity was not involved in their discovery and development.

However, the development of mianserin is another example of serendipitous influence. As part of a research program carried out by Organon International, B.V. in Oss (The Netherlands), mianserin (a tetracyclic piperazino-azepine) was synthesized in 1966 by van der Burg *et al*[78], with the aim of confirming whether the antihistamine properties of phenbenzamine and the anti-serotonergic activity of cyproheptadine could be combined in a chemical structure that could be potentially useful for treating asthma, migraine or allergic diseases such as hay fever.

Early pharmacological studies confirmed that mianserin was capable of antagonizing the effects of serotonin in different samples of various animal tissues[79], including human blood vessels, and exhibited antihistamine properties[80]. These findings led to the launch of a pilot study in 1969, which was not published, in which the tetracyclic compound was administered to 10 asthmatic patients compared to an untreated control group. Patients who received mianserin had significantly fewer night-time asthma attacks. However, this line of research was not continued as a number of central adverse effects, mainly sedation, were also described[81]. Nevertheless, another study in Ireland also in 1969, found that mianserin had a marked positive effect in improving mood in some subjects, and they began to call mianserin the "good mood pill." This observation about the hypothetical antidepressant properties of mianserin spurred on the clinical development of the molecule[81]. A number of experimental studies carried out using computer analyses of electroencephalogram recordings and comparative pilot trials with amitriptyline confirmed the antidepressant efficacy of this drug[82], which was presented as the first representative of a new generation of antidepressants (heterocyclic antidepressant compounds). Clinical trials over the next few years revealed antidepressant efficacy similar to that of classical TCAs, but superior to that of other "second generation" agents such as nomifensine or trazodone[81].

As in the case of the two group-leading agents of TCAs and MAOIs, mianserin falls within the type II pattern under our serendipitous attribution criteria, *i.e.* an initial serendipitous discovery when looking for an antihistamine drug leading secondarily to a non-serendipitous discovery of an antidepressant agent (Table 2).

NOTES FOR DIALOGUE

Serendipity is a phenomenon that has been regularly and constantly referred to when analyzing the great discoveries that supported the birth of modern psychopharmacology. But, as previously mentioned, the real role of serendipity in these processes has not been sufficiently well defined, possibly due to differences in opinion among authors given the semantic ambiguity of the term "serendipity" [83], and the degree of importance attributed at any given time to the two elements that make up the concept of serendipity: sagacity and unforeseen accidents. For this reason, our group[13,18] advocates the original meaning of the term, as "the discovery of something unexpected or not intentionally sought, in line with favors only the prepared mind"[35].

In fact, in the field of psychopharmacology, contrary to what has been postulated, pure serendipitous discoveries are rather rare, and most of them are of a mixed nature. Some authors refer to these patterns as "pseudo-serendipity"[84] or discoveries that are "serendipity analogues"[85].

These mixed serendipitous discoveries usually consist of a pattern that starts from an initial serendipitous observation and culminates in an intentionally sought-after discovery. For this reason, some authors and scholars may fall into the interpretative error of ascribing merit to chance or luck alone, seeing the results of research processes as a mere continuation of the initial serendipitous findings rather than as two manifestly different events. The cases presented in this paper on the discovery of the two families of classical antidepressants are proof of this: TCAs and MAOIs. Many other discoveries during the 1950s are included within this type II serendipitous attribution pattern that we have defined (initial serendipitous discoveries, in some cases made in laboratory animals, leading secondarily to non-serendipitous discoveries), such as the discovery of the antipsychotic properties of chlorpromazine and clozapine and the experimental tranquillizing properties of meprobamate and its subsequent anxiolytic effect in clinical trials. However, the clearest example was the discovery of the lethargic effect of lithium salts in guinea pigs and their subsequent antimanic effect in humans. Most authors consider the discovery of the antimanic effects of lithium to be purely serendipitous. However, Cade himself pointed out that the link between his casual observation of the lethargic effect in guinea pigs and the subsequent confirmation of the antimanic efficacy of lithium salts was far from obvious[86]. For more information on the historical development of these drugs, see the work of our group[19,20,23,25,41,87-89].

There are also examples of mixed serendipitous discoveries in reverse, included in our type III pattern (non-serendipitous discoveries partnered secondarily with serendipitous discoveries). The most representative example of this group would have to be barbiturates and their intended hypnotic effects,

which made the later serendipitous discovery of their anticonvulsant and antiepileptic effects possible [90].

But although serendipity does not usually work alone, there are also cases of pure serendipitous discoveries (type I pattern of attributability), such as the discovery of the anticonvulsant and mood stabilizing effects of valproic acid and valproate, respectively, or the discovery of the psychotropic effects of lysergic acid diethylamide. Similarly, other discoveries in the field of psychopharmacology during the golden decade of the 1950s should be included under the type IV pattern, namely non-serendipitous discoveries, in line with our operational definition of an unintended finding. Notable here is the discovery of the anxiolytic effect of chlordiazepoxide, the first benzodiazepine agent[91], and the antipsychotic effect of haloperidol and reserpine[24,92,93].

The clinical introduction of psychotropic drugs during the 1950s can be considered one of the great advances in medicine of the 20th century, and a major part of this breakthrough can be attributed to the discovery of the antidepressant effects of iproniazid and imipramine[3], a process in which serendipity played an essential role. But it is worth highlighting another series of contributions to the progress of biological psychiatry in addition to this great clinical contribution[3]. First, from a strictly pharmacological point of view, the development of imipramine led to the introduction of new methods for assessing the antidepressant activity of different substances[94]. Second, the discovery and subsequent therapeutic use of TCAs and MAOIs played a major role in developing the first etiopathogenic theories on affective disorders[95]. During the 1960s, catecholaminergic theories of depression blossomed, postulating a functional impairment of brain noradrenergic neurotransmission as the primary cause of affective disorders based on observations made on the effects of newly discovered antidepressant drugs, such as the blocking of synaptic reuptake of norepinephrine by imipramine[96]. Later, in 1968, Carlsson *et al*[97] described for the first time how imipramine was able to block the reuptake of serotonin in brain pathways, thereby laying the groundwork for the "serotonergic hypothesis" of depression.

However, the story of these two families of antidepressants evolved in completely different ways. Consequently, while TCAs continue to be used in clinical practice in an important way and constitute first-line tools in clinical research, MAOIs have suffered a large reduction in their use, except in the specific case of atypical depressions, largely due to their problems of interactions with other psychostimulant drugs and with tyramine-rich foods, which can lead to tragic hypertensive crises. However, despite this divergence, the importance of imipramine and iproniazid in the history of psychopharmacology is paramount.

CONCLUSION

It is clear that during the 1950s and 1960s serendipity played an important role in the process of building modern psychopharmacology in general and the first groups of families of antidepressant drugs in particular giving way in later decades to another way of understanding scientific research in this field, namely the systematic and rational planning of projects to be developed. In recent decades, psychopharmacology is moving away from the influence of serendipity towards new scientific approaches, although this is a gradual process[98] as can be seen with the serendipitous introduction of ketamine into the antidepressant arsenal. In any event, the results of this work confirm that serendipity should be understood as more of an eminently scientific construct than a literary curiosity.

In the words of the discoverer of vitamin C, Albert Szent-Györgyi, "discovery consists of seeing what everybody has seen and thinking what nobody has thought"[99].

FOOTNOTES

Author contributions: All authors have contributed to this work; López-Muñoz F and Álamo C designed the study; López-Muñoz F and Guerra JA analyzed the data; López-Muñoz F, D'Ocón P and Romero A wrote the manuscript; López-Muñoz F approved the final manuscript; all authors reviewed and approved the final draft.

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ORIGINAL ARTICLE

Observational Study

Dimensional (premenstrual symptoms screening tool) *vs* categorical (mini diagnostic interview, module U) for assessment of premenstrual disorders

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Abstract

BACKGROUND

Premenstrual syndrome (PMS) is the constellation of physical and psychological symptoms before menstruation. Premenstrual dysphoric disorder (PMDD) is a severe form of PMS with more depressive and anxiety symptoms. The Mini international neuropsychiatric interview, module U (MINI-U), assesses the diagnostic criteria for probable PMDD. The Premenstrual Symptoms screening tool (PSST) measures the severity of these symptoms.

AIM

To compare the PSST ordinal scores with the corresponding dichotomous MINI-U answers.

METHODS

Arab women (n = 194) residing in Doha, Qatar, received the MINI-U and PSST. Receiver Operating Characteristics (ROC) analyses provided the cut-off scores on the PSST using MINI-U as a gold standard.

RESULTS

All PSST ratings were higher in participants with positive responses on MINI-U. In addition, ROC analyses showed that all areas under the curves were significant

with the cutoff scores on PSST.

CONCLUSION
This study confirms that the severity measures from PSST can recognize patients with moderate/severe PMS and PMDD who would benefit from immediate treatment.

Key Words: Premenstrual symptoms screening tool; Premenstrual dysphoric disorder; Arabs; Categorical *vs* dimensional classification

Core Tip: This manuscript assesses the relationship between responses on the dichotomous the Mini international neuropsychiatric interview, module U (MINI-U) answers and the scores on the Premenstrual Symptoms screening tool (PSST). Our findings give reassurance that the MINI-U provides an adequate assessment for the probable diagnosis of Premenstrual dysphoric disorder (PMDD) and that the severity measures of the PSST can recognize patients with moderate/severe premenstrual syndrome and PMDD who would benefit from immediate treatment.

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INTRODUCTION

Premenstrual syndrome (PMS) is characterized by a collection of mild to severe physical, affective, and behavioral symptoms experienced by many reproductive age women. The symptoms occur cyclically before or during the luteal phase of the menstrual cycle. During this period, the symptoms might cause impairment to the daily lives of women, disrupting both work and personal activities[1]. Premenstrual dysphoric disorder (PMDD) is a more severe form of PMS with a greater emphasis on depressive and anxiety symptoms[2]. PMS and PMDD usually resolve within a few days of menstruation. The etiology of PMS and PMDD is not clearly understood, but the onset of symptoms is associated with hypersensitivity to changes in the ovarian hormonal level during the menstrual cycle, dysregulated immune function[2], neurotransmitter dysregulation, stress, diet and lifestyle[3-5]. Treatment intervention is mostly tailored to the patient's symptoms profile because the cause of PMS and PMDD is unknown. Conventional nonpharmacological treatments are lifestyle interventions such as improved diet, increased exercise, sleep hygiene, and Cognitive Behavioral Therapy (CBT) for stress management. Pharmacological interventions include analgesic treatment, combined oral contraceptives[6], and selective serotonin reuptake inhibitors[7].

Overall, 75%-85% of women have experienced PMS symptoms[1,8], whereas PMDD affects 5%-8% of reproductive age women worldwide[9]. According to the International Classification of Diseases (ICD-10)[10], only one distressing symptom at the time of menstruation is required for PMS diagnosis. It does not consider the severity of the symptoms, and no clear definition exists when PMS becomes clinically significant. Contrarily, diagnosis of PMDD mandates the impairment of functioning by the symptoms [11]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[12], the criteria for the diagnosis of PMDD are: (1) At least five symptoms must be present in the final week before the onset of menses and resolve within a few days of the onset of menses, and these symptoms must occur in the majority of the menstrual cycles; (2) At least one symptom must be marked affective lability, marked irritability or anger or marked depressed mood or anxiety; (3) One or more of the following symptoms must be present: decreased interest in usual activities, difficulty in concentration, increased fatigue, change in appetite, marked change in sleep, feeling overwhelmed or physical symptoms; and (4) These symptoms should affect productivity at work or school, relationships, responsibilities, or social activities. These symptoms should not be attributable/resultant to symptoms from: (1) Another psychiatric disorder; or (2) Physiological effects of a substance. Finally, these symptoms should be confirmed by prospective daily ratings for at least two symptomatic cycles.

The Mini International Neuropsychiatric Interview (MINI) is a structured interview consisting of several modules developed to establish a diagnostic instrument that is easy to administer, inexpensive, highly sensitive, and specific to diagnose DSM-IV-TR psychiatric disorders[13,14]. Module U (MINI-U) is the corresponding module that categorically measures the presence or absence of symptoms to fulfill

diagnostic criteria for PMDD[15]. Prospective daily ratings have to be completed for at least two symptomatic cycles to confirm the diagnosis. Thus, they are the only way to measure severity and monitor symptoms over time[16]. However, completing daily ratings proved to be difficult in practice [17,18].

The Premenstrual Symptoms screening tool (PSST) is an instrument that includes all premenstrual symptoms and a measure of impairment as per DSM-IV-TR criteria. It also translates categorical DSM-IV-TR criteria into a dimensional rating scale to assess severity[16]. Thus, it is a useful diagnostic tool to capture moderate/severe PMS and PMDD diagnoses in symptomatic women who would benefit from treatment[19]. The Arabic version of PSST was already validated, where it showed good consistency and reliability (Cronbach's alpha = 0.92). The discriminant validity showed adequate specificity (95.6%) but low sensitivity (26.7%), indicating that PSST is a good screening tool to confirm the cases with true PMDD where treatment is possibly indicated. The positive and negative values (PPV and NPV) for PMDD were 85.2% and 58.3%, respectively. The construct validity was assessed using exploratory factor analysis, and the results showed that the original 19 items (14 questions on the symptoms and five on the interference with daily activities) of the PSST were grouped into five factors accounting for 66.73 % of the variance[20].

The MINI-U for diagnosis of PMDD relies mainly on the presence or absence of symptoms, including the impact on functioning. At the same time, PSST uses a dimensional scale to measure the severity of symptoms which ultimately is very important to determine the effects of symptoms on daily activities. Unfortunately, no studies compared the diagnostic categorical scales with dimensional measures of severity of PMDD symptoms. Such comparisons would enhance the accuracy of the psychometric measures of the combined approaches when diagnosing and monitoring patients with moderate/severe PMS and PMDD. Furthermore, the availability of valid cut-off scores from PSST tested through answers from MINI-U (DSM criteria) would give more confidence to diagnose PMDD based on the severity measures of PSST. This reassurance would facilitate the initiation of treatment for this group of patients instead of waiting two months, especially that the daily recording of symptoms has proven to be very difficult in practice[17,18]. Thus, the aims of this study were: (1) To compare the responses between the dichotomous MINI-U answers and the scores on the PSST items; and (2) To establish the cut-off scores on the dimensional PSST items by using the categorical MINI-U as a gold standard.

MATERIALS AND METHODS

This cross-sectional study is part of a project to validate the Arabic version of the PSST[20]. This article reports a secondary analysis of the relationship between answers on the Arabic MINI-U with the corresponding items in the Arabic PSST (see Table 1).

Study setting and subjects

The study took place in Doha, Qatar, a country experiencing rapid development and economic growth. As a result, the Qatari population includes many expatriate residents from different nationalities and ethnicities. However, the most stable populations are the Qatari and Arabs, representing respectively 15% and 13% of the population[21]. Arab women were recruited at two Primary Healthcare Centers between October 2013 and March 2014.

Participants were eligible to join the study if they were Arab females between 18 and 45 years old and with a regular menstrual cycle of 24 to 32 d. The following exclusion criteria were adopted to control other confounding conditions: women taking oral contraceptive pills, hormonal therapy, psychotropic medication, and suspected of being pregnant or in menopause. In addition, women with endometriosis, acute thyroid or pituitary disorders, or any other acute medical problem were ineligible to participate. Lastly, women with a history of drug and alcohol abuse or an active psychiatric disorder (other than PMDD), diagnosed in the previous six months, were excluded.

During the recruitment period, a total of 430 women were approached in primary healthcare centers to join the study. After an initial screening, 280 women were eligible for the study and agreed to learn more about the research project. However, only 194 women agreed to participate and were consented to join the study. Following consent, a further 15 participants were excluded from the study: 4 participants were pregnant, 4 elected to withdraw from the study, 4 participants spoke Arabic but were not originally from an Arab country, and 3 participants were excluded due to another possible psychiatric diagnosis as per the MINI screen. Therefore, the sample consisted of 179 female participants who completed all study procedures. This sample size was sufficient to detect the projected sensitivity or specificity of 85 percent and an estimated prevalence of severe PMS/PMDD of 20 percent, within a margin of error of 10 percent and a 95 percent confidence interval. This sample size was sufficient to detect the projected sensitivity or specificity of 85 percent and an estimated prevalence of severe PMS/PMDD of 20 percent, within a margin of error of 10 percent and a 95 percent confidence interval.

Research design

This study is cross-sectional with no interventions, and all participants provided written consent before

Table 1 Corresponding items between premenstrual symptoms screening tool and the Mini-premenstrual dysphoric disorder

Symptom	PSST	MINI-U
Anger/irritability	1	U3 - D
Anxiety/tension	2	U3 - B
Tearful/sensitive to rejection	3	U3 - C
Depressed mood /hopelessness	4	U3 - A
Decreased interest in work activities	5	U3 - E
Decreased interest in home activities	6	U3 - E
Decreased interest in social activities	7	U3 - E
Difficulty concentrating	8	U3 - F
Fatigue/lack of energy	9	U3 - G
Overeating/food cravings	10	U3 - H
Insomnia	11	U3 - I
Hypersomnia	12	U3 - I
Feeling overwhelmed or out of control	13	U3 - J
Physical symptoms	14	U3 - K
Symptoms interfered with:		
Work efficiency/productivity	A	U2
Relationship with co-workers	B	U2
Relationship with family	C	U2
Your social life activities	D	U2
Home responsibilities	E	U2
Most menstrual periods of last year are preceded by significant mood changes for almost one week	-	U1

PSST: Premenstrual Symptoms screening tool; MINI-U: The Mini International Neuropsychiatric Interview, Module U.

enrollment. The Institutional Review Boards of Hamad Medical Corporation and Weill Cornell Medicine in Doha, Qatar, approved this study. A licensed physician or nurse interviewed participants to confirm their eligibility. The psychiatrists then administered the Arabic Mini International Neuropsychiatric Interview Plus version 6 (MINI-Plus 6) to screen for any psychiatric disorders, including PMDD (MINI-U) as per DSM-IV-TR criteria[15]. An independent second rater, blinded to the results of the MINI, collected sociodemographic information, past medical and psychiatric history, smoking and exercise patterns, and administered the PSST. The independent raters were medical students or nurses who were formally trained to administer and rate the PSST. A good inter-rater agreement was established before the collection of data. A pilot sample (20 women) was assessed independently by more than two raters, and the interclass coefficient was 0.89.

Procedures

Recruitment for this study commenced shortly after the introduction of DSM-5. However, no diagnostic instruments were available at the time to diagnose PMDD according to DSM-5 criteria; hence we used the MINI-U that followed DSM-IV-TR criteria. DSM-5 adopted the same criteria for the diagnosis of PMDD as DSM-IV-TR except for minor modifications. The only major shift is the recognition of PMDD as a distinct diagnostic entity in DSM-5[12], whereas it was classified as a Mood Disorder Not Otherwise Specified in DSM-IV-TR[22].

Module U in the MINI is a screening and diagnostic tool for PMDD. It is composed of 13 dichotomous questions (U1, U2, and U3-A to U3-K) (Table 1) with the possibility of answering "yes" or "no." The first two questions respectively assess mood changes before menstruation and if the subject experienced any difficulty at work or in usual activities and relationships during these periods. The last set of questions determines the presence of affective, behavioral, and physical symptoms using lettered questions U3-A to U3-K, as indicated in Table 1. A diagnosis of probable PMDD is reached if the first two questions U1 and U2, are answered positively together with at least one affective symptom from U3-A to U3-D and also four of the questions U3-A to U3-K were answered[14,22].

Table 2 Sociodemographic characteristics

Variables	
Mean age (SD), yr	32.12 (8.26)
Country born, *n* (%)	
Qatar	111 (62.0)
Other	68 (38.0)
Marital status, *n* (%)	
Married	112 (62.6)
Never married	55 (30.7)
Divorced/widowed	12 (6.7)
Education level, *n* (%)	
Elementary or intermediate school	11 (6.2)
Secondary or high school	53 (29.9)
Vocational/associate degree	55 (31.1)
University degree or postgraduate degree	58 (32.7)
Employment status, *n* (%)	
Employed	118 (66.6)
Housewife	25 (14.1)
Jobseeker	11 (6.2)
Student	15 (8.5)
Retired	2 (1.1)
Other	6 (3.4)
Lifestyle, *n* (%)	
Current cigarettes smoker	5 (2.8)
Current shisha smoker	9 (5.1)
Regular exercise	55 (30.7)

SD: Standard deviation.

Table 3 Clinical features of subjects

Medical Characteristics, *n* (%)	
PMS, according to PSST	63 (35.2)
PMDD according to PSST	25 (13.9)
PMDD according to MINI	84 (46.7)
Previous diagnoses	
Psychiatric diagnosis	6 (3.3)
Depression	9 (5.0)
Chronic lung disease	25 (13.9)
Hypertension	7 (3.9)
Cardiac disease	5 (2.8)
Arthritis	20 (11.1)
Osteoporosis	9 (5.0)

Kidney disease	4 (2.2)
Diabetes	10 (5.6)
Hypercholesterolemia	20 (11.1)
Cancer	2 (1.1)
Allergies	52 (28.9)

PMS: Premenstrual syndrome; PSST: Premenstrual Symptoms screening tool; PMDD: Premenstrual dysphoric disorder.

The PSST is composed of two sections representing the two domains as per DSM-IV-TR criteria for PMDD. The first section includes a list of 14 questions related to premenstrual symptoms, followed by the second section of 5 questions that measure the severity of interference of the symptoms on a woman's ability to function (Table 1). Responses are reported on a severity scale of "not at all," "mild," "moderate," or "severe," corresponding to a score of 1 to 4 in our study. The following criteria must be present for the diagnosis of PMDD: (1) At least one of the responses to questions 1-4 is severe; (2) In addition at least four of 1-14 questions are moderate to severe; and (3) At least one of A, B, C, D, E is severe. Also, the following criteria must be present for a diagnosis of moderate to severe PMS: (1) At least one of the responses to questions 1-4 is moderate to severe; (2) In addition at least four of 1-14 questions are moderate to severe; and (3) At least one of A, B, C, D, E is moderate to severe[16]. The original author[16] and McMaster University approved the translation of the PSST. The PSST was translated to Arabic using the repeated forward-backward procedure. All concerns were resolved by modifying the Arabic version of PSST until the original author approved the English back-translated version. Please refer to the study by Mahfoud *et al* for further details on the translation and validation procedures for the Arabic versions[20].

Statistical analysis

All analyses were performed using IBM Statistical Package for Social Sciences (SPSS) for Mac version 24 [23]. The level of significance was set at 5%. Sociodemographic characteristics and clinical features were reported as means and standard deviations (SD) for continuous measures such as age and as frequency and percentage for categorical measures such as education level. To compare the scores on the PSST items by MINI-U responses (Yes *vs* No), we reported the median and interquartile range (IQR), and we used the Wilcoxon-Mann-Whitney test to determine if the PSST severity measures are valid to differentiate between those who answered Yes *vs* No on MINI-U. Bonferroni correction (an option in SPSS) was used to correct for the multiple comparisons. The comparisons were followed by receiver operating characteristics (ROC) analyses using the MINI-U answers as the gold standard to determine the cut-off scores on the PSST, in addition to their sensitivity and specificity measures. Finally, we used the highest Youden indices (J) to determine the best cut-off scores on each item in PSST and the corresponding sensitivity and specificity[24].

RESULTS

Sociodemographic and clinical characteristics

A total of 179 female participants completed all study procedures. The study sample had a mean age of 32.12 years (SD = 8.26). The majority of participants were born in Qatar (62.0%), married (62.6%), and employed (66.6%). Approximately 33% of participants had a university degree, and 31% practiced regular exercise. According to the PSST, 14% of participants had a PMDD diagnosis, and 35% had PMS. However, according to MINI-U, 49% of participants had a diagnosis of probable PMDD. A minority of participants had been diagnosed in the past with depression (5%) or other psychiatric illness (3.3%) (Tables 2 and 3).

Frequency of symptoms as per MINI-U and PSST

According to the symptoms assessed by the PSST, the most common severe symptoms were anger or irritability (31.3%), physical symptoms (23%), and being tearful or sensitive to rejection (20.8%). The most common moderate symptoms reported by our participants were physical symptoms (36.5%), anger or irritability (34.6%), and fatigue or lack of energy (27.4%). The severity of these symptoms mainly affected their relationships with their family (moderate, 20.2% and severe 9%) and their work efficiency or productivity (moderate, 19.7% and severe 7.3%). The symptoms that our participants least experienced were feeling overwhelmed or out of control (57.4%), insomnia (58.4%), and difficulty concentrating (53.6%). According to the MINI-U, the most common symptoms were physical symptoms (86.7%), fatigue or lack of energy (74.4%), and anger or irritability (73.3%). The least reported symptoms were difficulty concentrating (31.7%), and feeling overwhelmed or out of control (36.7%) (Table 4).

Table 4 Frequency of symptoms as per the Mini international neuropsychiatric interview, module U and premenstrual symptoms screening tool

	MINI-U (Yes)	Not at all	Mild	Moderate	Severe
PSST symptoms	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Anger/irritability	132 (73.3)	23 (12.8)	38 (21.2)	62 (34.6)	56 (31.3)
Anxiety/tension	98 (54.4)	57 (32.0)	46 (25.8)	46 (25.8)	29 (16.3)
Tearful/sensitive to rejection	97 (53.9)	83 (46.6)	26 (14.6)	32 (18.0)	37 (20.8)
Depressed mood/hopelessness	104 (57.8)	78 (43.8)	40 (22.5)	35 (19.7)	25 (14.0)
Decreased interest in work activities	83 (46.1)(All three)	65 (36.3)	52 (29.1)	41 (22.9)	21 (11.7)
Decreased interest in home activities		53 (29.8)	55 (30.9)	44 (24.7)	26 (14.6)
Decreased interest in social activities		79 (44.1)	49 (27.4)	30 (16.7)	21 (11.7)
Difficulty concentrating	57 (31.7)	96 (53.6)	53 (29.6)	21 (11.7)	9 (5.0)
Fatigue/lack of energy	134 (74.4)	47 (26.9)	56 (32.0)	48 (27.4)	24 (13.7)
Overeating/food cravings	98 (54.4)	92 (51.7)	27 (15.2)	25 (14.0)	34 (19.1)
Insomnia	95 (52.8)(Both)	104 (58.4)	36 (20.2)	21 (11.8)	17 (9.6)
Hypersomnia (needing more sleep)		76 (42.7)	39 (21.9)	33 (18.5)	30 (16.9)
Feeling overwhelmed or out of control	66 (36.7)	101 (57.4)	22 (12.5)	37 (21.0)	16 (9.1)
Physical symptoms	156 (86.7)	16 (9.0)	56 (31.5)	65 (36.5)	41 (23.0)
Symptoms interfered with:					
A - Work efficiency/productivity	94 (52.2)(Altogether)	85 (47.8)	45 (25.3)	35 (19.7)	13 (7.3)
B - Relationship with co-workers		108 (61.4)	41 (23.3)	19 (10.8)	8 (4.5)
C - Relationship with family		69 (38.8)	57 (32.0)	36 (20.2)	16 (9.0)
D - Your social life activities		89 (50.0)	49 (27.5)	29 (16.3)	11 (6.2)
E - Home responsibilities		89 (50.0)	55 (30.9)	23 (12.9)	11 (6.2)

PSST: Premenstrual Symptoms screening tool; MINI-U: The Mini international neuropsychiatric interview, module U.

Scores on PSST items by MINI-U dichotomous responses

We used the Wilcoxon-Mann-Whitney test to assess if the ordinal scores on the PSST items are different between those who answered Yes vs. No on the MINI-U. Among the MINI-U dichotomous answers, all PSST ratings were significantly higher among participants who answered Yes ($P < 0.01$). Participants who answered "No" on the MINI-U had a median score of 1 (Not at all) for all the symptoms except for: (1) Anger or irritability; (2) Anxiety or tension; (3) Decreased interest in home activities; and (4) Physical symptoms where the median rating was 2 (mild). Participants who answered "Yes" had a median score from 1.5 (not at all to mild) to 3 (moderate). Out of the 14 symptoms assessed, nine had a median score of 3 (moderate), four symptoms had a median rating of 2 (mild), and one symptom had a median rating of 1.5 (not at all to mild) (Table 5). The median rating of the interference of these symptoms on work or productivity, relationship with family, relationship with co-workers, relationship with family, on social life activities, and home responsibilities was 2 (mild) (Table 5).

Cut-off scores on PSST items by MINI-U dichotomous responses

ROC analyses showed that all areas under the curves were significant with the cut-off scores (and the corresponding sensitivity and specificity values using the Youden index) on the corresponding PSST items using the MINI-U questions as the gold standard. The cut-off scores for the items on anger or irritability, anxiety or tension, decreased interest in work or home activities, overeating, hypersomnia, and physical symptoms were 2.5 on the corresponding PSST items. The remaining items had a corresponding cut-off score of 1.5. The balanced sensitivity and specificity values for all the corresponding cut-off scores were adequate, ranging from 0.50 to 0.83 (Table 6).

Table 5 Scores on Premenstrual Symptoms screening tool items by the Mini international neuropsychiatric interview, module U dichotomous responses

	MINI-U				
	No		Yes		
PSST	Median	IQR	Median	IQR	*P* value[1]
Anger/irritability	2	2	3	1	< 0.001
Anxiety/tension	2	1	3	2	< 0.001
Tearful/sensitive to rejection	1	0	3	2	< 0.001
Depressed mood/hopelessness	1	1	2	2	< 0.001
Decreased interest in work activities	1	1	3	1	< 0.001
Decreased interest in home activities	2	1	3	1	< 0.001
Decreased interest in social activities	1	1	3	1	< 0.001
Difficulty concentrating	1	1	2	1	< 0.001
Fatigue/lack of energy	1	1	2	1	< 0.001
Overeating/food cravings	1	1	2	2	< 0.001
Insomnia	1	1	1.5	2	0.004
Hypersomnia (needing more sleep)	1	1	3	3	< 0.001
Feeling overwhelmed or out of control	1	1	3	2	< 0.001
Physical symptoms	2	2	3	2	< 0.001
Symptoms interfered with:					
Work efficiency/productivity	1	1	2	2	< 0.001
Relationship with co-workers	1	0	2	2	< 0.001
Relationship with family	1	1	2	1	< 0.001
Your social life activities	1	1	2	2	< 0.001
Home responsibilities	1	1	2	2	< 0.001

[1]Wilcoxon-Mann-Whitney test was used to compare the PSST severity scores.
PSST: Premenstrual Symptoms screening tool; MINI-U: The Mini international neuropsychiatric interview, module U.

DISCUSSION

The first aim of this study was to compare the responses between the dichotomous MINI-U answers and the scores on the PSST items. Our study showed a discrepancy in the prevalence of PMDD diagnosis between the MINI criteria (46.7%) and PSST criteria (13.9%). The discrepancy between the two could be attributed to the dichotomous nature of MINI-U questions that assess only the presence or absence of symptoms. At the same time, those in PSST focus more on the severity of symptoms to establish PMDD diagnosis. The high prevalence of PMDD is also higher than that reported worldwide (5%-8%)[9]. Other countries such as Iran[25], Jordan[8], India[26], and Brazil[27] reported a similarly high prevalence of PMDD suggesting that there are ethnic variations in the prevalence of PMDD. It also highlights the need for an efficient and valid diagnosis of PMDD to recognize these patients and initiate treatment as early as needed. In comparing the participants who answered positively vs. negatively on the MINI questions, we found that all PSST symptom ratings were significantly higher among those who answered positively. Furthermore, most symptoms on PSST had a median rating of "moderate," indicating clinical significance (Table 5). The PSST severity measures might allow distinguishing which symptoms are clinically significant. Previous studies reported that 20% of women have subthreshold PMDD and can benefit from further monitoring and treatment[28]. The most commonly reported moderate/severe symptoms for our population were anger/irritability, anxiety, and physical symptoms (Table 4). These were also common complaints among Jordanian and Emirati women[29,30]. One of the major concerns with the MINI and PSST is the requirement to have daily ratings of symptoms for a minimum of two cycles per DSM criteria to confirm the cyclical presence of symptoms for moderate/severe PMS and PMDD. Keeping a daily diary before initiating treatment may cause resistance for women to seek treatment. In research settings, an epidemiological study found that 30% of

Table 6 The cut-off scores of the Premenstrual Symptoms screening tool items with the corresponding the Mini international neuropsychiatric interview, module U items

Symptom	PSST	MINI-U	AUC	95%CI	*J*	Cut-off	Sensitivity	Specificity
Anger/irritability	1	U3 - D	0.804[a]	(0.73-0.88)	0.48	2.5	0.780	0.696
Anxiety/tension	2	U3 - B	0.740[a]	(0.67-0.81)	0.41	2.5	0.608	0.800
Tearful/sensitive to rejection	3	U3 - C	0.835[a]	(0.77-0.90)	0.63	1.5	0.814	0.812
Depressed mood/hopelessness	4	U3 - A	0.735[a]	(0.66-0.81)	0.38	1.5	0.718	0.658
Decreased interest in work activities	5	U3 - E	0.752[a]	(0.68-0.83)	0.45	2.5	0.590	0.860
Decreased interest in home activities	6	U3 - E	0.743[a]	(0.67-0.82)	0.39	2.5	0.602	0.783
Decreased interest in social activities	7	U3 - E	0.768[a]	(0.70-0.84)	0.43	1.5	0.795	0.634
Difficulty concentrating	8	U3 - F	0.806[a]	(0.74-0.88)	0.55	1.5	0.842	0.706
Fatigue/lack of energy	9	U3 - G	0.728[a]	(0.64-0.81)	0.36	1.5	0.823	0.535
Overeating/food cravings	10	U3 - H	0.700[a]	(0.62-0.78)	0.36	2.5	0.495	0.861
Insomnia	11	U3 - I	0.614[a]	(0.530.70)	0.17	1.5	0.500	0.671
Hypersomnia	12	U3 - I	0.732[a]	(0.66 0.81)	0.39	2.5	0.537	0.852
Feeling overwhelmed or out of control	13	U3 - J	0.714[a]	(0.63 0.80)	0.39	1.5	0.667	0.722
Physical symptoms	14	U3 - K	0.723[a]	(0.60 0.85)	0.33	2.5	0.643	0.682
Symptoms interfered with:								
Work efficiency/productivity	A	U2	0.696[a]	(0.62 0.77)	0.32	1.5	0.677	0.639
Relationship with co-workers	B	U2	0.674[a]	(0.60 0.75)	0.30	1.5	0.527	0.771
Relationship with family	C	U2	0.686[a]	(0.61 0.76)	0.30	1.5	0.753	0.542
Your social life activities	D	U2	0.729[a]	(0.65 0.80)	0.38	1.5	0.677	0.699
Home responsibilities	E	U2	0.724[a]	(0.65 0.80)	0.40	1.5	0.688	0.711

[a]$P <$ 0.01. PSST: Premenstrual Symptoms screening tool; MINI-U: The mini international neuropsychiatric interview, module U; AUC: Area under the curve; CI: Confidence interval; *J*: Youden index.

women refused to participate in a study because they did not want to fill daily ratings, and the latter is usually associated with a high dropout rate[31]. Our results suggest that the severity measures of PSST can capture the PMDD cases with significantly severe symptoms who would benefit from treatment initiation.

The study's second aim was to establish the cut-off scores on the dimensional PSST items by using the categorical MINI-U as a gold standard. All the cut-off scores showed significant differentiation and ranged from 1.5 to 2.5 with adequate sensitivity and specificity (Table 6). The MINI-U is a diagnostic instrument, whereas the PSST is a diagnostic and dimensional instrument[16]. However, both scales are based on DSM-IV-TR criteria for diagnosing PMDD and thus are assessing the same symptoms (Table 1). The concordance between these instruments showed that most symptoms corresponding to a "Yes" in the MINI-U had a cut-off score of 1.5 or a rating of at least 'mild' on the corresponding PSST items. On the other hand, affirmative answers to anger/irritability, anxiety/tension, decreased interest in home activities, and physical symptoms in the MINI-U had a corresponding cut-off score of 2.5 or at least 'moderate' symptoms in the PSST, meaning that the latter captured mainly the moderate to severe cases. However, the challenge is distinguishing which women need treatment from those whose symptoms are not clinically relevant[31]. Moderate/severe PMS and PMDD are poorly diagnosed and mostly untreated conditions[32]. Furthermore, women with moderate/severe PMS symptoms have a higher rate of work absences and increased medical expenses[1]. Therefore, these women can benefit from a prompt referral and timely treatment[1].

Limitations

This study has many strengths, like its design and applying the validated Arabic dimensional PSST with the Arabic equivalent categorical scale MINI. Still, a few limitations can affect the results of our study. The sample size is probably not large enough to cover the representation of the multiple Arabic countries and the potential variability in PMDD presentation in different countries. It is worth adding

that the cut-off scores on PSST are based on retrospective symptoms, and DSM requires daily records for two consecutive months to confirm the diagnosis. Thus, further validation of the significant and relevant cut-off scores on PSST against future prospective recordings is necessary to confirm the utility of using the dimensional PSST in the early treatment of PMDD as defined in the categorical DSM.

CONCLUSION

In conclusion, our results showed a significant relationship between the Arabic MINI-U and PSST responses, providing evidence to support that the PSST is a practical measure for PMDD. Participants who answered positively on the MINI had significantly higher ratings and relevant cut-off scores on the corresponding PSST items. Thus, this study reassures that the MINI-U provides an adequate assessment for the probable diagnosis of PMDD. Furthermore, the severity measures of the PSST can recognize patients with moderate/severe PMS and PMDD who would benefit from immediate treatment. Thus, there is a clear advantage of using PSST to early identify these patients with moderate/severe symptoms who clinically cannot wait for the daily measures of MINI-U. In addition, these patients with significant mood symptoms can benefit from treatment with selective serotonin inhibitors[33]. However, prospective studies are still needed to confirm the validation scores and comply with the DSM criteria.

ARTICLE HIGHLIGHTS

Research background

Premenstrual symptoms (PMS) are very common in child-bearing women and include several physical and emotional symptoms lasting for one week before menstruation. The premenstrual dysphoric disorder consists of the symptoms of PMS and, more significant depressive symptoms that affect the functioning of women. Some instruments measure the severity of these symptoms (Premenstrual Symptoms screening tool, PSST). Others assess the presence or absence of these symptoms and are usually used to diagnose if the premenstrual symptoms recur over two consecutive cycles (Mini international neuropsychiatric interview, module U).

Research motivation

As required by the Diagnostic and Statistical Manual of Mental Disorders, the daily recording of symptoms over two months is challenging to comply with regularly. Further, women might not receive the proper treatment if no adequate assessment or diagnosis is made. We believe that using appropriate scales like PSST that measures the severity of symptoms can be validated as tools for diagnosis.

Research objectives

To compare the scores of both PSST and MINI module U. We also calculated the cut-off scores on the dimensional PSST items by using the categorical MINI-U as a gold standard.

Research methods

We recruited eligible women from primary care centers. Two blinded raters independently administered the dichotomous Arabic MINI module U and the Arabic PSST to women. We compared the scores on the PSST items by MINI-U responses (Yes *vs* No) using the median and interquartile range. To determine the cut-off scores on the PSST (including sensitivity and specificity measures), we used the receiver operating characteristics analyses using the MINI-U answers as the gold standard.

Research results

According to the MINI-U, the most common symptoms were physical symptoms (86.7%), fatigue or lack of energy (74.4%), and anger or irritability (73.3%). Out of the 14 symptoms assessed, nine had a median score of 3 (moderate), four symptoms had a median rating of 2 (mild), and one symptom had a median rating of 1.5 (not at all to mild). Among the MINI-U dichotomous answers, all PSST ratings were significantly higher among participants who answered Yes ($P < 0.01$). The cut-off scores for the items on anger or irritability, anxiety or tension, decreased interest in work or home activities, overeating, hypersomnia, and physical symptoms were 2.5 on the corresponding PSST items. The balanced sensitivity and specificity values for all the corresponding cut-off scores were adequate, ranging from 0.50 to 0.83.

Research conclusions

Our results suggest that the severity measures of PSST can capture the PMDD cases with significantly severe symptoms who would benefit from treatment initiation. Furthermore, women with moderate/severe PMS symptoms have a higher rate of work absences and increased medical expenses.

These women can, therefore, benefit from a prompt referral and timely treatment.

Research perspectives

Larger prospective studies are needed to further validate the utility of cut-off scores from PSST to confirm the diagnosis and justify the initiation of treatment.

FOOTNOTES

Author contributions: Hassen A and Rana E designed the research; Rifka C performed the research; Ziyad M and Rifka C analyzed the data; all authors wrote the paper.

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SYSTEMATIC REVIEWS

Lidocaine in fibromyalgia: A systematic review

Jozélio Freire de Carvalho, Thelma L Skare

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Abstract

BACKGROUND

Fibromyalgia (FM) patients are treated with antidepressants, and in most cases, these drugs lose efficacy or present side effects. Intravenous lidocaine (IL) is an anesthetic drug used in some FM trials.

AIM

To systematically review the safety and efficacy of IL in FM patients.

METHODS

To systematically search PubMed for articles in English, Spanish, and Japanese with English Abstracts on FM and lidocaine between 1966 and February 2021. This study was registered at PROSPERO.

RESULTS

We found only ten articles published in this field, with a total of 461 patients. Females predominated varying from 95% to 100% in the studies. Age varied from 40.9 to 55 years old. Disease duration varied from 1 mo to 6.4 years. Lidocaine dose varied from 2 to 7.5 mg/kg *via* intravenous infusion. Follow-up period varied from 65.7 to 90 days. Regarding outcomes, most studies used the visual analogue scale (VAS) for pain; before short-term lidocaine administration, VAS was between 6.1 and 8.1 and after treatment was between 1.7 and 4.5 mm. Concerning long term lidocaine, VAS varied from 30% to 35.4% after lidocaine infusion. Side effects were observed in 0% to 39.6% of cases, they were usually mild or moderate.

CONCLUSION

This study demonstrates the short-term effectiveness and safety of intravenous lidocaine in FM patients. However, more studies, including long-term follow-up, are still needed.

Key Words: Lidocaine; Fibromyalgia; Pain; Intravenous infusions

Core Tip: This is the first systematic review on lidocaine studies in fibromyalgia patients.

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INTRODUCTION

Fibromyalgia is a painful chronic disease characterized by diffuse pain for over three months with associated co-morbidities including headaches, irritable bowel syndrome, anxiety, depression, and others[1]. FM is the third most common musculoskeletal condition and may affect 0.4% (in Greece) to 8.8% (in Turkey) of a population and has a global prevalence of 2.7%[1].

Standard treatments for FM include physical exercise, psychological intervention, and medication. Regarding pharmacological treatment, antidepressants are the leading choice for this condition. However, adverse effects can lead to dropouts, which range from 9% to 23% in short-term studies and from 11.4% to 27.2% in long-term studies[2]. Lack of efficacy is also observed during FM treatment, which can reach between 50 to 60% of cases[2]. Thus, different treatment modalities are desired for unresponsive patients or who present side effects with drugs.

Lidocaine is a topical anesthetic drug used worldwide to treat specific clinical situations such as systemic sclerosis. It is used intravenously in chronic pain and arrhythmia cases[3]. Intravenous lidocaine has been shown to control the symptoms of diabetic neuropathy[4]; there are some studies on intravenous lidocaine use in FM patients with controversial results[5-14].

In light of this, the objective of this article is to perform a systematic review of the safety and efficacy of lidocaine in FM patients.

MATERIALS AND METHODS

Literature review

We performed a systematic search of articles published in PubMed/MEDLINE, Web of Sciences, LILACS, and Scielo from 1966 to November 2020 using the following MeSH entry terms: "lidocaine" and "fibromyalgia." We used equivalent strategies in other databases. All related articles are based on "lidocaine" and "fibromyalgia" without language restriction. The reference lists in the selected articles were analyzed to identify other publications. Initially, two authors (JFC and TLS) performed the literature search and independently selected the study abstracts. In the second stage, the same reviewers independently read the full-text articles selected by abstracts. Disagreements arising in consensus meetings were resolved by a third reviewer. The authors followed PRISMA guidelines[15]. We designed a standardized form to extract the following information from relevant articles regarding authors, year of publication, number of patients studied, demographic data, disease duration, study follow-up, pre- and post-intervention VAS, lidocaine posology, and outcomes (Figure 1).

This study was registered at PROSPERO under number CRD42021227210.

RESULTS

Demographic and clinical data and pre- and post-lidocaine treatment VAS scores for FM patients are shown in Table 1.

There were only ten articles published in this field, with a total of 461 patients. Females predominated varying from 95% to 100% in the studies. Age varied from 40.9 to 55 years old. Disease duration varied from 1 month to 6.4 years.

Lidocaine IV dosage varied from 2 to 7.5 mg/kg. Follow-up was from 65.7 to 90 d.

Regarding outcome, most studies evaluated VAS. Before lidocaine, VAS ranged from 6.1 to 8.1 and after treatment, from 1.7 to 4.5 mm in the short term. Concerning long term after lidocaine infusion,

Table 1 Clinical and demographic characteristics of the xx studies on fibromyalgia and lidocaine treatment

Ref.	Study design	N, female sex	Age, yr	Disease duration	Follow-up	Lidocaine prescription	Concomitant treatment	Short-term VAS,		Long-term VAS		Other outcomes	Adverse effects
								Pre and post lidocaine	Pre and post, placebo	Pre and post lidocaine	Pre and post placebo		
Verd *et al* [5]	Prospective	48, 95.8%	Median age-55		90 d	Escalating dose from 2 mg/kg to 5 mg/kg per day, IV during 10 d	-	Pain measured by BPI 29.5→26.5	-	In 90 d BPI = 30.0	-	Improved in MOS and EXPEC; Short-lived improvement in BPI, BFI and depression	Nausea (n = 8); Worsening pain (n = 1)
Wilderman *et al*[6]	Retrospective	74, 9.7%	51.3	NA	5 mg/kg→65.7 d; 7.5 mg/kg→86.3 d; 7.5 mg/kg→90.9 d	Escalating doses: 5 mg/kg, 7.5 mg/kg and 7.5 mg/kg + magnesium 2.5 g IV	None	Δ VAS in 5 mg/kg = 2.41; Δ VAS in 7.5 mg/kg = 3.15; Δ VAS in 7.5 mg/kg + Mg = 3.62	NA	Pain relief:In 30.2% of 5 mg/kg-median time 62 d; In 39.1% in 7.5 mg/kg; median time 62.5 d; 40.6% in 7.5 mg/kg + Mg; Median time 64 d	NA	-	24/222 infusions (10.8%)-dizziness, nausea, hyperglycemia, headache, lip numbness and mild dyspnea
Kim *et al*[7]	Retrospective	55, 94.5%	NA	NA	After 1 infusion	5 mg/kg (maximum of 500 mg), IV		7.6 ± 1.6→5.8 ± 2.2	-	-	-	Caucasians and non-smokers had better results	NA
Albertoni Giraldes *et al*[8]	RCT	42, 95%	42.4 ± 9.4	6.0 ± 5.05	8 wk	250 mg/wk – for 4 wk IV; *vs* saline	Amitriptyline 25 mg, paracetamol if needed.	6 ± 1.3 3.9 ± 2.8	7.2 ± 1.3→2.7 ± 2.9	-	-	IL-1, IL-6 and IL-8 values did not change	Placebo equal to lidocaine: nausea, vomiting, drowsiness, paresthesia, constipation and dry mouth
Staud *et al* [9]	Prospective	62, 100%	45.8 ± 14.8	NA	Data collection just after injections	Group 1 (n = 20)- 4 injections of 50 mg lidocaine, IM; Group 2 (n = 21)- 2 injections 50 mg lidocaine + 2 saline, IM; Group 3 (n = 21)- four	Muscle relaxing drugs and/or tricyclics were allowed	VAS declined 38%	-	-	-	Mechanical and heat hyperalgesia decreased significantly	NA

						injections saline, IM							
Vlainich *et al*[10]	RCT,	30, 100%	Group 1-40.9 ± 11.6; Group 2-44.7 ± 10.5	NA	4 wk	Group 1- (*n* = 15) lidocaine 240 mg/wk for 4 wk, IV; Group 2- (*n* = 15) Saline	Amitriptyline 25 mg	7.6 ± 0.8→4.1 ± 2.3	7.0 ± 1.2→4.0 ± 2.1	-	-	norepinephrine and serotonin levels unchanged dopamine levels ↑ week 4 in the placebo group.	No
Schafranski *et al*[11]	Prospective	23, 95.6%	NA	NA	4 wk	Sequential lidocaine infusions from 2-5 mg/kg for 5 d, IV	None	8.1 ± 1.7→6.8 ± 2.4	-	Mean VAS of pain = 7.1 ± 2.3 in 30 d	-	FIQ, HAQ improved significantly	No
Raphael *et al*[12]	Prospective and retrospective	106, 92% prospective arm (to see side effects); 50, 82%retrospective arm (to see efficacy)	51.4 prospective arm; 50.2 retrospective arm	Prospective arm- NA; 6.6 ± 4.5 yr in retrospective arm	N/A	Started at 5 mg/kg-100 mg and increased to 5 mg/kg+150 mg (maximum 550 mg) IV; For 6 consecutive days	None	Only in the retrospective arm 9→5; Mean duration pain relief 11.5 ± 6.5 wk	-		-	No improvement in work status; improvement in several sociological and psychological dimensions	Only in the prospective arm; 2 major effects: (pulmonary edema and supra ventricular tachycardia); 42/106 minor effects: Hypotension (*n* = 17); Headache (*n* = 8), hypertension (*n* = 5), tachycardia (*n* = 1), arrhythmia (*n* = 1), pulmonary edema (*n* = 1)
Bennett *et al*[13]	Prospective	10, 100%	44.2	16 (1-192) mo	4 wk	Started at 250 mg/d and increased by 50 mg/d to 500 mg/dfor 6 d, IV	Haloperidol 0.5 mg/d + clomipramine 10 mg/d or Amitriptyline 10 mg/d	8 4.1	-	Mean VAS of pain = 5.4 in 30 d	-	Stopped analgesics. Mood improved but not statistically significant	None
Sörensen *et al*[14]	Double blind, placebo-controlled	11, 100%	41, (range 21-59)	5 yr (range 2-11)	1 wk after 2nd injection	2 injections, IV; 5 mg/kg *vs* saline	Paracetamol or dextropropoxyphene	(VAS from 0-100); 6.1→4.5	(VAS from 0-100); 51→51	-	-	Tender points, muscle endurance and muscle strength (except dorsiflexors of wrist) unchanged	NA

VAS: Visual analogue scale from 0-10 except Sörensen *et al*[14], which was 0-100; Δ VAS: Difference in VAS pre and post infusions; IV: Intravenous; IM: Intra muscular; NA: Not available; RCT: Randomized controlled trial; IL: Interleukin, MOS: Medical outcome sleep scale; EXPEC: Patient'S expectations; BPI: Brief pain inventory; BFI: Big five inventory.

VAS varied 30% to 35.4%.

Side effects were observed in 0% to 39.6% of cases, usually with mild or moderate repercussions. These effects were dizziness, nausea, vomiting, hyperglycemia, headache, lip numbness, mild dyspnea, paresthesia, dry mouth, and increasing pain. The significant effects were pulmonary edema and supraventricular tachycardia.

DISCUSSION

This is the first study to systematically review the therapeutic effects of intravenous lidocaine in FM patients.

The study strengths are: (1) The inclusion of studies with patients with international criteria for FM; and (2) The exclusion of case reports, case series, and observational studies. Prospective studies present a higher degree of evidence.

The analgesic properties of intravenous lidocaine were first observed in 1962 when used to treat postoperative pain[16]. Thirty-six years later, a study demonstrated that lidocaine might be used to treat postoperative pain, reducing hospital stay in patients who had undergone radical prostatectomy[17]. Lidocaine acts by blocking sodium channels on the neuronal membrane that may play a role in the pathogenesis of inflammatory and neuropathic pain[6].

Previous studies have demonstrated the efficacy of intravenous lidocaine in FM patients. Bennett and Tai[13] described improvement in pain scores were maintained even 30 d after lidocaine infusion. Furthermore, Sörensen *et al*[14] evaluating 12 fibromyalgia patients showed improvements in VAS pain scores during and 15 min after a 30 min infusion of lidocaine in a double-blind placebo-controlled crossover study. Three of the 12 patients who responded to lidocaine had their pain reduced. The authors reported no statistically significant differences between FM and placebo groups in tender points, muscle strength (hip flexors and handgrip), and muscle endurance. However, the lidocaine group exhibited a significant improvement in wrist dorsiflexion muscle strength[14].

Raphael *et al*[12] conducted a prospective study of the adverse effects of lidocaine in 106 patients with FM and a retrospective questionnaire study of the efficacy of this drug in 50 FM patients. Serial infusions of IV lidocaine were administered for six consecutive days at 5 mg/kg minus 100 mg and increased by 50 mg/d to 5 mg/kg plus 150 mg over 6 h, with the maximum allowable dose being 550 mg. Pain was measured using an 11-point VAS, in a 4-point verbal scale of pain severity (none, mild, moderate, severe), and according to the average number of hours per day in pain. Pain relief was also measured on the 11-point VAS along with pain relief duration. The psychological and social impact of the pain were evaluated by measuring depression, coping ability, dependency, and several other items using the 11-point scales. Pain score and relief interruption, pain mean duration, and verbal assessment were significantly reduced following lidocaine treatment. Mean pain relief duration was 11.5 ± 6.5 wk, ranging from 0 to 36 wk. Psychosocial measurements significantly improved after lidocaine treatment in all parameters except work status.

Schafranski *et al*[11], in an open trial, showed similar results after five sequential lidocaine infusions with rising dosages (2-5 mg/kg, days 1-5). The Fibromyalgia Impact Questionnaire (FIQ) and a VAS for pain were applied before lidocaine infusion and immediately, and 30 d after the 5th infusion. They observed significant reductions in FIQ and VAS after the fifth infusion which were maintained after 30 d [11].

Finally, some limitations were observed in our study. For instance, no comparison between lidocaine and classical antidepressants used in FM were available in literature. The number of participants was low and future studies should include large patient samples with more long-term follow-up; this would enable a better understanding of the course of this therapeutic modality in FM.

CONCLUSION

The present study was a systematic review of all prospective studies that evaluated the role of lidocaine in FM patients and found excellent short-term efficacy. Future studies using larger FM patient samples and long-term follow-up which address the safety and efficacy of lidocaine are needed.

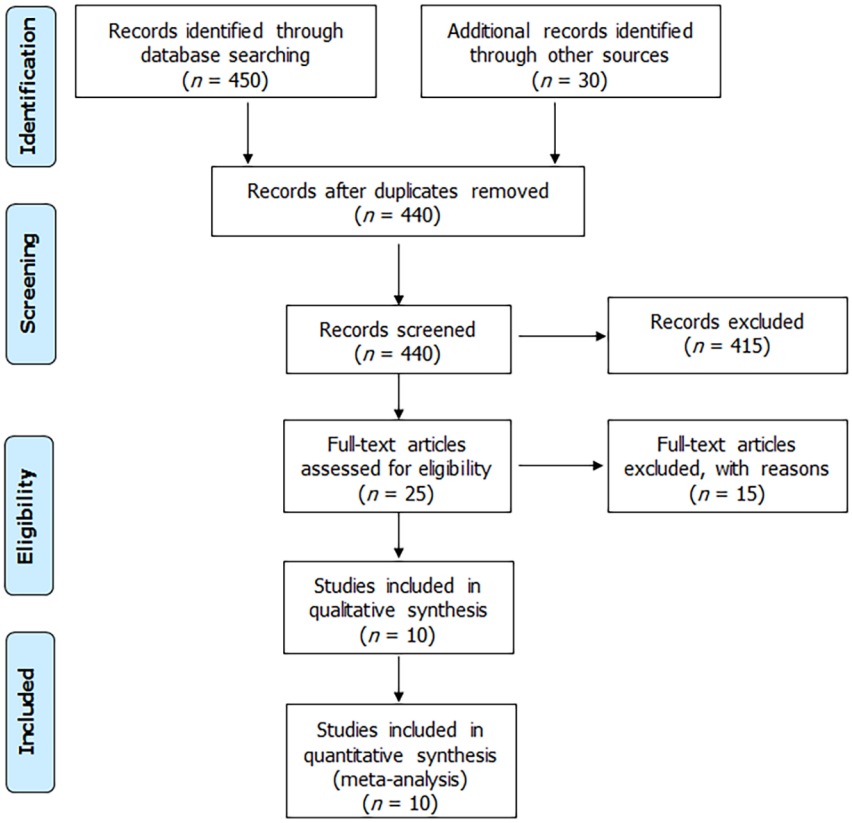

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Figure 1 Flow chart of included articles, following PRISMA.

ARTICLE HIGHLIGHTS

Research background

Lidocaine is used to treat fibromyalgia patients.

Research motivation

As there are some articles that evaluated the role of lidocaine as therapy of fibromyalgia patients, the authors thought it is important to systematically review this literature.

Research objectives

The authors had the objective to perform the first systematic review on lidocaine in the treatment of fibromyalgia.

Research methods

Systematic review based on PRISMA guidelines and PROSPERO register.

Research results

Most studies showed reduction of pains measured by visual analogic scale after lidocaine infusion.

Research conclusions

This systematic review showed that lidocaine is effective and safe for fibromyalgia treatment, mainly in short-term.

Research perspectives

Future studies with large number of participants to evaluate the safety and efficacy of lidocaine for fibromyalgia is needed, as short and long-term studies.

FOOTNOTES

Author contributions: de Carvalho JF and Skare TL contributed equally to this work; de Carvalho JF and Skare TL designed the research study, performed the research, and analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

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SYSTEMATIC REVIEWS

Psychiatric comorbidities in cancer survivors across tumor subtypes: A systematic review

Anne Bach, Klara Knauer, Johanna Graf, Norbert Schäffeler, Andreas Stengel

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Abstract

BACKGROUND

Psychiatric disorders are common but underdiagnosed in cancer survivors. Research suggests that tumor type has an effect on the prevalence of clinically relevant depression, anxiety, comorbid anxiety-depression and posttraumatic stress disorder (PTSD).

AIM

To identify studies that examined the prevalence of clinically relevant levels of depression, anxiety, comorbid anxiety-depression and PTSD for patients with one or more tumor sites and compare those prevalences between cancer subtypes.

METHODS

Four databases (PubMed, PsycInfo, PubPsych and the Cochrane Database) were searched and resulted in a total of 2387 articles to be screened. To be included, a study must have investigated cancer-free and posttreatment survivors using tools to assess clinically relevant levels of the listed psychiatric comorbidities. All articles were screened by two authors with a third author reviewing debated articles.

RESULTS

Twenty-six studies on ten different tumor types fulfilled all inclusion criteria and were included in the review. The studies showed heterogeneity regarding the study characteristics, number of participants, time since diagnosis, and assessment tools. Generally, all four comorbidities show higher prevalences in cancer survivors than the general population. Brain tumor survivors were reported to

have a relatively high prevalence of both depression and anxiety. Studies with melanoma survivors reported high prevalences of all four psychiatric comorbidities. Regarding comorbidities, a wide range in prevalence existed across the tumor types. Within one cancer site, the prevalence also varied considerably among the studies.

CONCLUSION

Psychiatric comorbidities are more frequent in cancer survivors than in the general population, as reflected by the prevalence of depression, anxiety, comorbid anxiety-depression and PTSD across all tumor subtypes. Developing generalized screening tools that examine psychological distress in cancer survivors up to at least ten years after diagnosis could help to understand and address the psychological burden of cancer survivors.

Key Words: Cancer survivor; Cancer type; Prevalence; Psychiatric disorder; Psychiatric comorbidity; Survivorship; Tumor site

Core Tip: Psychiatric disorders are a common comorbidity in cancer survivors, even years after diagnosis. Studies have found that tumor type has an effect on the prevalence of clinically relevant depression, anxiety, comorbid anxiety-depression and posttraumatic stress disorder. This systematic review compared the prevalence of these four psychiatric disorders in cancer survivors among tumor types. The results suggest that there are variations in the prevalence of all comorbidities across and within cancer types. A future direction should be the development of a screening tool to regularly assess cancer survivors' psychological distress for at least 10 years after the initial disease.

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INTRODUCTION

Before, during and after treatment, patients with cancer are exposed to a variety of factors (physical constraints, fatigue, financial problems, *etc*.) that may impact their psychological state. This is in addition to the possible trauma caused by a cancer diagnosis and treatment. With the number of cancer survivors growing due to longevity and medical progress, the evaluation of long-term psychological aftereffects and their predispositions becomes more relevant[1]. Over the last decades, the examination of psychiatric comorbidities in cancer survivors has become a growing research field. According to several studies, tumor type can have an impact on the risk of developing a psychiatric comorbidity[2-4]. This paper aimed to review the literature about psychiatric comorbidities in cancer survivors across cancer types to identify their commonalities and differences.

Cancer survivors experience several challenges even after finishing acute treatment. Chemotherapy, radiation and other kinds of treatment often bear the risk of long-term side effects. This can lead to clinically relevant levels of psychological distress, and survivors have an increased risk for mood alterations compared to the general population[5]. The simultaneous presence of two or more clinical conditions is referred to as comorbidity, which requires special attention when strategizing treatment [6]. Some of the most frequent psychiatric comorbidities in long-term cancer survivors are depression, generalized anxiety disorder and posttraumatic stress disorder (PTSD), all of which can depend on the type of cancer.

The response to each cancer type calls for unique treatment plans and exposes survivors to a particular risk of recurrence. Therefore, cancer survivors of different tumor types are exposed to several burdens, not only during the acute treatment phase but also after the treatment is finished. Studies have found that patients with specific tumor types may experience more psychological distress than others. Muzzatti *et al*[4] found that survivors with a history of breast cancer showed more anxiety and depression than those with a history of lymphoma or genitourinary tumors. Similarly, Götze *et al*[3] described that breast and skin cancer survivors showed the highest levels of anxiety and depression, whereas prostate cancer survivors showed the lowest levels. Another study showed significant variation in psychological distress across cancer types[7]. In contrast, there are studies that did not find a significant difference between cancer sites and clinical levels of depression, anxiety or PTSD[8-10]. In these studies, other patient characteristics, such as sex and age at the time of diagnosis, were proposed

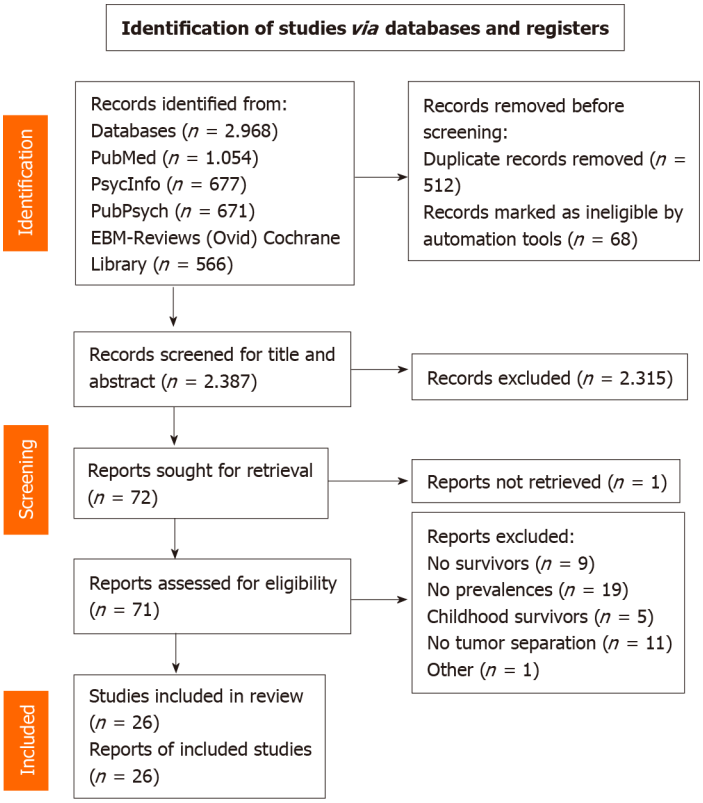

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Figure 1 PRISMA flow diagram.

to have an influence on the prevalence of psychiatric comorbidities. Another argument by Deimling *et al* [10] is that with increasing time since diagnosis, cancer type and treatment-specific stressors are removed, and psychological stressors become more homogeneous.

Identifying whether there are specific influences on distress depending on a survivor's cancer site could help to identify necessary adjustments to survivorship programs and medical follow-up treatments. To do so, it is important to know which patient characteristics and tumor entities have an effect on psychological distress and further effects on the development of psychiatric disorders due to disease-related burdens. Additionally, this could provide more insight into cancer site-specific psychological guidelines for the psychological care of cancer survivors after treatment.

Therefore, this systematic review aimed to identify studies that examined clinically relevant levels of depression, anxiety, comorbid anxiety-depression and PTSD across tumor types.

MATERIALS AND METHODS

The systematic review was conducted according to the PRISMA statement criteria[11]. The review protocol is registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42021253430).

Literature search

We searched four databases between February 8th and 19th, 2021: PubMed, PsycInfo, PubPsyc and the Cochrane Database. Articles published in any year were included. Our search terms were as follows: [(Psychiatric OR psych*) AND (comorbidity OR disorder)] AND (cancer OR tumor OR neoplasm OR oncolog*) AND (survivor OR survivorship OR long-term).

Inclusion and exclusion criteria

The eligibility criteria were based on the five PICOS dimensions. P: The participants were cancer survivors with the following characteristics: Adults at the time of cancer diagnosis and not in (primary) acute treatment. Survivors were defined according to the World Health Organization (WHO) as patients who have had cancer and are, following treatment, now cured of the disease[12]. This implies that all studies where all/a subpopulation(s) of survivors were still in active treatment were excluded. I: Studies with any kind of intervention were excluded. C: A control group was not necessary. O: The outcomes

Table 1 Assessment tools

Assessment tool		Used in study (No. of occurrences)
EDS	Edinburgh Depression Scale	1 (1)
HADS	Hospital Anxiety and Depression Scale	1, 3, 5, 6, 8, 9, 15, 19, 21, 22, 23 (11)
SCID	Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders	1, 22, 23, 26 (4)
PTSD-(inventory) scale	Self-report scale based on DSM-III-R criteria with items corresponding to PTSD symptoms	2, 16 (2)
SCL-90	Symptom Checklist 90	2 (1)
PCL-C/PCL-S	Posttraumatic Stress Disorder Checklist-Civilian Version/Posttraumatic Stress Disorder Checklist-Specific	3, 5, 13, 14 (4)
UW-QOL	The University of Washington Quality of Life instrument - brief, self-administered questionnaire to analyze rates of depression	11 (1)
IES	Impact of Event Scale	7, 20 (2)
BDI	Beck Depression Inventory	4, 18, 20 (3)
PHQ-9	Patient Health Questionaire-9	10, 17 (2)
GAD-7	Generalized Anxiety Disorder 7	10, 17, 24 (3)
GDS-SF/GDS-15	Geriatric Depression Scale-Short Form/Geriatric Depression Scale-15	12, 25 (2)
DASS	Depression-Anxiety-Stress-Scale	24 (1)
MINI	Mini International Neuropsychiatric Interview	4 (1)
SAI	Spielberger State Anxiety Inventory	20 (1)

EDS: Edinburgh Depression Scale; HADS: Hospital Anxiety and Depression Scale; SCID: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders; PTSD: Posttraumatic stress disorder; SCL-90: Symptom Checklist 90; PCL-C: Posttraumatic Stress Disorder Checklist-Civilian Version; PCL-S: Posttraumatic Stress Disorder Checklist-Specific; UW-QOL: The University of Washington Quality of Life; IES: Impact of Event Scale; BDI: Beck Depression Inventory; PHQ-9: Patient Health Questionaire-9; GAD-7: Generalized Anxiety Disorder 7; GDS-SF: Geriatric Depression Scale-Short Form; GDS-15: Geriatric Depression Scale-15; DASS: Depression-Anxiety-Stress-Scale; MINI: Mini International Neuropsychiatric Interview; SAI: Spielberger State Anxiety Inventory.

were the prevalence of psychiatric comorbidities, more specifically, the clinically relevant levels of depression, anxiety, comorbid anxiety-depression and PTSD. S: The study designs included in the review were observational, cross-sectional and longitudinal designs.

The exclusion criteria were: (1) Studies with no cancer patients; (2) Studies with no survivors; (3) Studies with no psychiatric/psychological assessment; (4) Studies with a patient group < 18 years old at the time of cancer diagnosis; (5) Studies not in accordance with the predefined study designs; (6) Articles with missing information or not written in English; (7) Studies including an intervention; and (8) Studies that did not separate the different tumor types.

Data extraction

After removing duplicates, the articles were screened for relevant titles by two authors. For papers where the first two authors did not agree, a third author decided. The remaining articles were screened for abstracts again by the two authors, with the third author reviewing debated articles. Then, all three authors came to a consensus. One author screened the remaining articles for the full texts. The studies that were considered eligible were included in the review, and the relevant data were extracted.

Quality assessment

The quality of each study was assessed according to the study design, participant selection and method of patient evaluation[13].

Statistical analyses

The included papers showed high heterogeneity in the number of participants, time since diagnosis and assessment tools used (Table 1). Furthermore, there were a limited number of articles per tumor site (*e.g.*, 4 articles related to breast cancer *vs* 1 article related to brain tumors). Therefore, this review aimed to perform a descriptive data analysis rather than a meta-analysis. The descriptive analysis focused on the prevalence of the mentioned psychiatric comorbidities in cancer survivors with a focus on similarities and differences among the tumor types.

RESULTS

The literature search of the four scientific databases provided 2968 results. After removing duplicates, 2387 articles were left for screening. Title screening reduced the number to 102 articles, which was further filtered to 72 for full text screening. Finally, 26 studies were considered relevant to the topic and were included in the review (Figure 1). Table 2 shows the extracted data (reference, tumor type, study population, time since diagnosis, screening tools to assess psychiatric comorbidity, prevalence of comorbidity and potential bias) of the included articles. Several studies had to be excluded after full text screening because of missing reports of the prevalence in percentages and instead reporting the mean results of the questionnaires.

Quality assessment

The studies included in the review were assessed for possible risks of bias. The natures of the study designs analyzed here are known to favor certain biases[13]. Table 2 shows the reviewed studies with the study design (self-report questionnaire, personal interview, *etc.*) and possible type of bias. All studies used a cross-sectional design, with only some having a matched comparison group, and therefore bear the risk of selection bias. Two qualities of the reviewed studies presented a risk of response bias: Cancer survivors with specific (psychological or physical) symptoms may be more likely to respond to a study invitation, and most studies were self-report questionnaires. Performance bias may have occurred in the studies that used personal interviews. Exclusion bias may be present in the studies where a specific group of participants was not included in the results (Table 2).

Study characteristics

There was a wide range of study characteristics within the included articles. We extracted data for ten different broad tumor sites. For each site, the number of articles included were as follows: Breast (5), gynecological/cervical (2), hematological (4), testicular (5), prostate (1), head and neck (3), stomach (1), melanoma (3), brain (1) and lung (1). The number of participants ranged between 17[13] and 1260[14]. The studies were published between 2002 and 2020. The age of the participants ranged between 18 and 93 years. Seven studies included only women, and six studies included only men because of the specificity of the cancer site. The remaining thirteen studies included both men and women.

Assessment tools

In the studies, psychiatric comorbidities were evaluated with a variety of assessment tools, including questionnaires and personal interviews. Table 1 shows all the assessment tools and their abbreviations with regard to the study they were used in. The most common questionnaire was the Hospital Anxiety and Depression Scale (HADS), which was used in eleven of the 26 studies. The assessment tool used in each article is shown in the summary of the findings (Table 2). Most articles included the screening of more than one psychiatric comorbidity (*e.g.*, depression and anxiety), while others focused on only one.

Time since diagnosis

The studies included in this review ranged from 144 d[16] to more than 11 years since diagnosis[17-19]. Some studies found an effect of time since cancer diagnosis and psychological distress. According to Mols *et al*[20], depressive symptoms declined over time, whereas anxiety scores stayed stable across a 4-year period.

Depression

Twenty-one of the 26 articles assessed the prevalence of depression in cancer survivors, including all ten tumor sites. Table 3 shows the studies organized by tumor site and the extracted percentages for clinical levels of depression. Comparing the prevalences among tumor types, a high variability, between 7.9% and 48%, can be seen. Whereas most tumor sites showed a range between 8% and 22% for clinical levels of depression, four cancer subtypes showed a much higher prevalence (above 40%): Head and neck[21], stomach[22], melanoma[14] and brain[23] cancer.

Furthermore, within one cancer site, the prevalence varied. For testicular cancer survivors, the prevalence of depression was relatively stable across the four studies included in the review (between 7.9%[19] and 9.7%[15,24]). For patients with breast cancer, the prevalence varied between 8%[16] and 22%[25].

Anxiety

Fifteen of the eligible studies assessed the prevalence of clinical levels of anxiety in cancer survivors. Among these, six different tumor types were assessed: Breast, testicular, hematological, cervical/gynecological, melanoma and brain tumors (Table 3). The percentage for anxiety ranged between 3.5% and 58.5%. A study on brain tumor survivors showed a high prevalence of clinical levels of anxiety of almost 60%[23], whereas across the other tumor sites, the prevalence ranged between 6.1%[19] and 20.2%[15].

Table 2 Summary of findings for included articles, organized by tumor subtypes

No.	Ref./country	Tumor site	Number of participants/gender/age in years	Time since diagnosis	Parameters and tests (related to psychiatric disorders)	Key results: Prevalence of clinical levels of: Anxiety/depression/PTSD/comorbid anxiety-depression	Possible bias
1	Alexander *et al* [26], 2010; United Kingdom	Breast	*n* = 200; 100% female; mean: 58.1, range: 29-89	Mean time since last treatment: 10.1 mo	EDS; HADS; SCID	Depression: 9%; anxiety: 3.5%; comorbid: 1.5	Selection bias; response bias
2	Amir *et al*[28], 2002; Israel	Breast	*n* = 39; 100% female; range: 37-60	≥ 5 yr	PTSD-scale; SCL-90	Full PTSD: 18%; partial PTSD: 56% (additional)	Selection bias; response bias
3	Mehnert *et al* [25], 2008; Germany	Breast	*n* = 1083; 100% female; mean: 61.8, range: 31-81	Average: 47 mo	HADS; PCL-C	Moderate to high anxiety: 38% (high: 20.1%); moderate to high depression: 22% (high: 11.3%); PTSD: 12%	Selection bias; response bias
4	Qiu *et al*[42], 2012; China	Breast	*n* = 505; 100% female; mean: 52.02	Mean time after surgery: 17.6 mo	BDI; MINI	Depression: 20.59%	Response bias; performance bias
5	Vazquez *et al* [16], 2020; United States	Breast	*n* = 700; 100% female; median: 37, range: 17-40	144 d: HADS; 30 mo (PCL-S)	PCL-S; HADS	PTSS: 6.3%; depression: 8%; anxiety: 23%	Selection bias; response bias
6	Dahl *et al*[24], 2005; Norway	Testicular	*n* = 1408; 100% male; mean: 44.6	Mean: 11.3 yr	HADS	Anxiety: 19.2%; depression: 9.7%; comorbid: 6.8%	Selection bias; response bias
7	Dahl *et al*[17], 2016; Norway	Testicular	*n* = 1418; 100% male; mean: 44.6	Mean: 11 yr	IES	Full PTSD: 4.5%; partial PTSD: 6.4%; probable PTSD (combination of the 2): 10.9%	Selection bias; response bias
8	Fosså *et al*[43], 2003; Norway	Testicular	*n* = 791; 100% male; median: 44, range: 23-75	Median: 12 yr	HADS	Anxiety: 19%; depression: 9%	Selection bias; response bias
9	Thorsen *et al* [15], 2005; Norway	Testicular	*n* = 1260; 100% male; median: 42	Mean: 11 years	HADS	Anxiety: 20.2%; depression 9.7%	Selection bias; response bias
10	Vehling *et al*[19], 2016; Germany	Testicular	*n* = 164; 100% male; mean: 44.4	Mean: 11.6 yr	GAD-7; PHQ-9	Anxiety: 6.1%; depression: 7.9%	Selection bias; response bias
11	Chen *et al*[33], 2013; United States	Head and neck	*n* = 211; 58% male; median: 57, range: 21-93	Disease free at least 1 yr	UW-QOL	Depression: 17%	Response bias
12	Lambert *et al* [21], 2005; United States	Head and neck	*n* = 694; 84.6% male; mean: 61.8	At least 6 mo	GDS-SF	Depression: 44.1%	Selection bias; response bias
13	Moschopoulou *et al*[44], 2018; United Kingdom	Head and neck	*n* = 93; 58.1% male; mean: 66	Mean: 6 yr	PCL-C	PTSD: 11.8%	Selection bias; response bias
14	Black *et al*[45], 2005; United Kingdom	Hodgkin's lymphoma non-Hodgkin's lymphoma; acute leukemia	*n* = 36; 50% female; adults	? - complete remission	PCL-C	PTSD: 17%	Selection bias; response bias
15	Daniëls *et al*[46],	Hodgkin's	*n* = 180; 55% male;	Mean: 4.6	HADS	Anxiety: 23%; depression: 18%	Selection

	2014; The Netherlands	lymphoma	median: 46	yr			bias; response bias
16	Geffen *et al*[35], 2003; Israel	Hodgkin's lymphoma; non-Hodgkin's lymphoma	HD: *n* = 8; nHL: *n* = 36; 46% male; median: 51; range: 27-80	At least 2 yr after treatment completion	PTSD-inventory scale	Full or partial PTSD: 32%; full PTSD: 18%; partial PTSD: 13% (additional)	Selection bias; response bias
17	Kuba *et al*[47], 2019; Germany	Hematological	*n* = 922; 57% male; range: 18-85	3 yr	PHQ-9; GAD-7	Anxiety: 9%; depression: 15%	Selection bias; response bias
18	Han *et al*[22], 2013; Korea	Stomach	*n* = 391; 72.9% male; mean: 54.5	Mean (time since operation): 27.4 mo	BDI	Depression: 43.9%	Selection bias; response bias
19	Hanprasertpong *et al*[48], 2017; Thailand	Cervical	*n* = 700; 100% female; mean: 53	Completion of treatment 3 mo - 10 yr before study	HADS	Anxiety: 20.46%; depression: 9.44%	Selection bias; response bias
20	Urbaniec *et al* [18], 2011; Australia	Gynecological	*n* = 45; 100% female; mean: 56.7, range: 23-83	Mean: 4 yr; range: 0.9-11.6 yr	BDI-II; SAI; IES-Revised	Anxiety: 28.9%; depression: 20%; probable PTSD: 15.6	Selection bias; response bias
21	Krajewski *et al* [49], 2018; Germany	Melanoma	*n* = 561; 51.2% male; mean: 62.1	4 yr	HADS	Anxiety: 10.2%; depression: 10.3%	Selection bias; response bias
22	Rogiers *et al*[27], 2020; Belgium	Melanoma	*n* =25; 28% male; median: 58, range: 28-86	Median: 30 mo	SCID-IV-CV; HADS	HADS: Anxiety: 32%; depression: 20%; comorbid: 12%. SCID: PTSD: 48%; depression: 0%	Selection bias; response bias; performance bias
23	Rogiers *et al*[14], 2020; Belgium	Melanoma	*n* = 17; 29% male; median: 57, range: 33-86	Median: 5.6 yr	SCID-IV-CV; HADS	HADS: Anxiety: 35%; depression: 41%; comorbid: 30%. Interview: PTSD: 35%; depression: 11.76%	Selection bias; response bias; performance bias
24	Nicol *et al*[23], 2019; Australia	Brain	*n* = 65; 35.4% male; mean: 49.97; range: 22-75	Mean: 5.29 yr	DASS-Depression; GAD-7	Anxiety: 58.5%; depression: 43.1%	Selection bias; response bias
25	Recklitis *et al* [50], 2014; United States	Prostate	*n* = 693; 100% male; mean: 67.1	Range: 3-8 yr	GDS-15	Depression: 15%	Selection bias; response bias
26	Uchitomi *et al* [51], 2003; Japan	Lung	*n* = 212; 60.4% male; mean: 62.1, range: 22-83	1 mo after surgery	SCID, Revised; POMS scale	Depression: 8%	Selection bias; performance bias

EDS: Edinburgh Depression Scale; HADS: Hospital Anxiety and Depression Scale; SCID: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders; POMS: Profiles of Mood States; GDS-15: Geriatric Depression Scale-15; GAD-7: Generalized Anxiety Disorder 7; SCID-IV-CV: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Clinical Version; BDI: Beck Depression Inventory; SAI: Spielberger State Anxiety Inventory; IES: Impact of Event Scale; PHQ-9: Patient Health Questionaire-9; PTSD: Posttraumatic stress disorder; UW-QOL: The University of Washington Quality of Life; GDS-SF: Geriatric Depression Scale-Short Form; PCL-C: Posttraumatic Stress Disorder Checklist-Civilian Version; MINI: Mini International Neuropsychiatric Interview; PCL-S: Posttraumatic Stress Disorder Checklist-Specific.

Comorbid anxiety-depression

Only four of the 26 articles assessed the prevalence of comorbid anxiety-depression in cancer survivors (Table 3). The included tumor types were breast, testicular and melanoma (2 studies). The two studies assessing the prevalence in melanoma patients showed a prevalence of comorbid anxiety-depression in up to 40%[14] of survivors. The smallest prevalence was found in breast cancer survivors, with a study indicating a prevalence of comorbid anxiety-depression of 1.5%[26].

Table 3 Prevalence of psychiatric comorbidities in % sorted by tumor site

No	Tumor site	Key result in %				Ref.
		Depression	Anxiety	Comorbid anxiety-depression	PTSD	
1	Breast	9	3.5	1.5	-	Alexander *et al*[26], 2010
2		-	-	-	18	Amir *et al*[28], 2002
3		22	38	-	12	Mehnert *et al*[25], 2008
4		20.6	-	-	-	Qiu *et al*[42], 2012
5		8	23	-	6.3	Vazquez *et al*[16], 2020
6	Testicular	9.7	19.2	6.8	-	Dahl *et al*[24], 2005
7		-	-	-	4.5	Dahl *et al*[17], 2016
8		9	19	-	-	Fosså *et al*[43], 2003
9		9.7	20.2	-	-	Thorsen *et al*[15], 2005
10		7.9	6.2	-	-	Vehling *et al*[19], 2016
11	Head and neck	17	-	-	-	Chen *et al*[33], 2013
12		44.1	-	--	-	Lambert *et al*[21], 2005
13		-	-		11.8	Moschopoulou *et al*[44], 2018
14	Hematological	-	-	-	17	Black *et al*[45], 2005
15		18	23	-	-	Daniels *et al*[21], 1976
16		-	-	-	18	Geffen *et al*[35], 2003
17		15	9	-	-	Kuba *et al*[47], 2019
18	Stomach	43.9	-	-	-	Han *et al*[22], 2013
19	Cervical, gynecological	9.4	20.5	-	-	Hanprasertpong *et al*[48], 2017
20		20	28.9	-	15.6	Urbaniec *et al*[18], 2011
21	Melanoma	10.3	10.2	-	-	Krajewski *et al*[49], 2018
22		20	32	12	48	Rogiers *et al*[27], 2020
23		41	35	30	35	Rogiers *et al*[14], 2020
24	Brain	43.1	58.5	-	-	Nicol *et al*[23], 2019
25	Prostate	15	-	-	-	Recklitis *et al*[50], 2014
26	Lung	8	-	-	-	Uchitomi *et al*[51], 2003

PTSD: Posttraumatic stress disorder.

PTSD

Ten studies assessed PTSD in cancer survivors across 6 different tumor types. Whereas testicular cancer survivors showed a comparably low level of full PTSD with a prevalence of 4.5%[17], the two studies including melanoma patients showed numbers as high as 48%[14,27]. For breast cancer survivors, the prevalence ranged from 6.3%[16] to 18%[28].

DISCUSSION

This systematic review aimed to describe differences and commonalities between psychiatric comorbidities in cancer survivors across ten tumor types. Twenty-six studies that matched all the inclusion criteria and provided the prevalence of at least one of the four psychiatric comorbidities as a percentage were included.

Studies on psychological distress in cancer survivors found that there are risk factors for developing clinical levels of mood disorders. A systematic review on the prevalence of depression in breast cancer survivors reported several factors associated with depression: Fatigue, low income or poor financial status, low education level and younger age[29]. A review with testicular cancer survivors found that

poorer psychological health was related to living alone, being unemployed or having a low socio-economic status and experiencing worse symptoms/side effects[30].

We observed differences across the studies in the prevalence of psychiatric comorbidities after a cancer diagnosis, even when patients were no longer in treatment and there was no sign of disease recurrence. It was not clear whether these differences were partly caused by the type of cancer. Other factors, such as the time since diagnosis, participant demographics, and the assessment tool, may have similarly influenced the prevalence of clinical levels of depression, anxiety, and PTSD. Andrykowski *et al*[31] found a wide range of reported anxiety and depression levels in cancer survivors, which was due to challenges in identifying the rate of psychological distress in cancer survivors. One of the difficulties is the variation in detecting a psychiatric disorder due to the range of screening tools and criteria. The studies in this review used a variety of assessment tools. Furthermore, the studies demonstrated a wide range of sample sizes and participant demographics, including the risk factors mentioned above. The country of origin has similarly been shown to have an effect on cancer survivors' psychological distress. For example, a comparison between Hong Kong Chinese and German Caucasian women with breast cancer showed that greater unmet psychological needs were detected in Germany[32].

Depression

Our results show a higher prevalence of depression in cancer survivors than in the general population. Whereas some of the studies reported prevalences in the normal range, more than half of the prevalences were 15% or higher. Furthermore, one longitudinal study[33] found that the prevalence of depression did not differ significantly over the course of five years for head and neck cancer survivors. A comparison of cancer types regarding depression showed consistently lower levels of depression in testicular cancer survivors than in breast cancer survivors, where the prevalence varied from 8% to 22%. Patients with several tumor entities, namely, head and neck, stomach, melanoma and brain tumors, demonstrate higher levels of depression, between 41% and almost 50%, indicating the need for special support for these groups of cancer survivors.

Anxiety

Anxiety scores were reported by 15 studies and showed a very wide range of prevalences from 3.5% to almost 60%. Moreover, our review showed that anxiety prevalence was higher than the prevalence of clinical levels of depression. Similarly, among United States adults, data on anxiety disorders shows a higher prevalence than the prevalence of depression[34]. The highest prevalences of anxiety were seen in breast, melanoma and brain tumor survivors, although one study on breast cancer survivors reported a prevalence as low as 3.5%. The study by Nicol *et al*[23] with brain tumor survivors reported an especially high number of survivors showing clinically relevant levels of anxiety, with a prevalence of 58.5%.

Comorbid anxiety-depression

Comorbid anxiety-depression was assessed in only four of the 26 included studies. A useful comparison among cancer types is therefore difficult. In contrast to the two studies on breast and testicular cancer survivors that reported a prevalence of 1.5% and 6.8%, respectively, the prevalences in two studies with melanoma survivors were higher (up to 40%)[14,27]. For all three of the previously mentioned psychiatric comorbidities, melanoma survivors seemed to show relatively high prevalences, which might indicate a distinctive demand for psychological support for this survivor group.

PTSD

Ten studies examined posttraumatic stress syndrome in cancer survivors. Geffen *et al*[35] compared survivors who either had Hodgkin's disease or non-Hodgkin's lymphoma with a matched control group that had experienced at least one traumatic life event. They did not find significant differences between the survivors and control group in the occurrence of posttraumatic stress symptoms, suggesting that a cancer diagnosis might have the same impact as experiencing a traumatic event. Again, studies on melanoma cancer survivors showed a particularly high prevalence of PTSD (35% and 48%), which was assessed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Clinical Version, at a median time of 30 mo and 5.6 years after the diagnosis, respectively[14,27]. Another study investigated the occurrence of PTSD in testicular cancer survivors 11 and 19 years after diagnosis and found that the prevalence of clinically relevant PTSD symptomatology was reduced by more than half at the latter time point[17].

Limitations

This review contains some limitations, with the most obvious being the limited number of studies per cancer site. Since we employed stringent inclusion and exclusion criteria, many studies were not included in the review. It was important to include only cancer survivors based on the WHO definition, meaning that the survivors were not going through acute treatment. This exclusion criterion was chosen to ensure that the prognosis and side effects of the treatment were not likely to influence the results of a psychiatric assessment. Several studies included a noteworthy number of survivors who still received

some kind of treatment, from radiotherapy to immunotherapy[3,36]. This limitation is likely influenced by the lack of a unique definition of cancer survivorship[37], which may have complicated the literature search.

Some studies have already investigated psychiatric comorbidities across different cancer types[4,9]. These studies did not include the separate prevalences per tumor type in their papers and therefore could not be reported in this review. Several studies reported the mean results on the questionnaires; however, the prevalence of clinical levels of depression, anxiety or PTSD could not be extracted. This review focused on four types of psychiatric comorbidities in cancer survivors, which represent the most common mental health disorders. Less common psychiatric comorbidities, such as acute psychosis, are likely present in cancer survivors (although at very low prevalence) but were beyond the scope of this review. Future work should address these.

We explored the extracted data with a focus on differences among cancer types. The studies that were reviewed displayed a high heterogeneity in key study characteristics (*e.g.*, the number of participants, time since diagnosis, assessment tools), which may have had a significant influence on the results and was not considered in our review. The various screening tools possibly measure psychological distress and clinical relevance in a way that cannot be easily compared[31]. A systematic review on the HADS indicated that the assessment tool might underestimate true levels of anxiety and depressive symptoms because it does not include somatic symptoms[38]. This may have impacted the generalizability of the HADS-based results.

Future directions

The increased prevalence of clinical levels of psychological distress for cancer survivors remains an issue to be adequately addressed. Whereas many survivorship programs are being developed, the specific needs of cancer survivors depending on their own personal experiences have not yet been widely explored. Beutel *et al*[39] suggest general screening even 10 years after diagnosis, which would show the objective and subjective needs of each cancer survivor. Götze *et al*[40] supported this recommendation following their examination of emotional distress in cancer survivors. They compared a group of survivors five years after diagnosis with a group 10 years post-diagnosis and found no significant difference in emotional distress between the groups. However, a significant difference between tumor entities was detected, with breast and skin cancer survivors showing the highest levels of anxiety and depression and prostate cancer survivors showing the lowest levels. Furthermore, Kypriotakis *et al*[41] compared long-term cancer survivors of different tumor sites at four different time points. They found that cancer stage at the time of diagnosis was a significant predictor of initial depressive symptoms. Therefore, a future direction could be the development of screening tools to repeatedly measure cancer survivors' psychological distress up to 10 years after the last acute treatment phase. According to Beutel *et al*[39], such screening would include survivors who are below the threshold of a mental disorder but still have difficulties adjusting to being a cancer survivor.

CONCLUSION

The articles included in this review showed high heterogeneity in several study characteristics (the number of participants, time since diagnosis, assessment tools, *etc.*) and showed that psychological distress in survivors is dependent on multiple factors. We aimed to describe the differences among tumor types, which were limited by missing data and/or the lack of a clear definition for survivorship. More research is needed that evaluates the specific psychological needs of cancer survivors and how to address them in survivor programs. Future research should have a clear definition of cancer survivorship and take participant characteristics such as the tumor subtype, the time since diagnosis and demographics into account. Furthermore, our results strongly suggest future guidelines for psychiatric and distress screenings for at least ten years after a cancer diagnosis, even when there is no sign of recurrence.

ARTICLE HIGHLIGHTS

Research background

Psychiatric disorders are common but underdiagnosed in cancer survivors. Research suggests that tumor type has an effect on the prevalence of clinically relevant depression, anxiety, comorbid anxiety-depression and posttraumatic stress disorder (PTSD) symptoms.

Research motivation

Detecting differences in the prevalence of four common mental disorders that can occur as a comorbidity in cancer survivors might lead to a better understanding of cancer survivors' psychological distress. This might help to address the psychological concerns of cancer survivors more effectively.

Research objectives

The aim of this review was to identify studies in which clinically relevant levels of common mental disorders in cancer survivors were examined. The prevalence rates were compared among different cancer types.

Research methods

Four databases were searched for studies that investigated cancer-free, posttreatment survivors with screening tools that assess clinically relevant levels of four common mental disorders. Two authors screened all articles, with a third author reviewing debated articles.

Research results

Twenty-six studies were included in the article and indicated the prevalence of one or more of the four mental disorders. Ten different tumor types were examined in the included papers. Generally, all four comorbidities show higher prevalences in cancer survivors than in the general population. The studies showed heterogeneity regarding the study characteristics, number of participants, time since diagnosis, and assessment tools. Each comorbid disorder had a variable prevalence across tumor subtypes. Within one cancer site, the prevalence also varied considerably among the studies.

Research conclusions

Psychiatric comorbidities are high in cancer survivors relative to the general population, as reflected by the prevalences of depression, anxiety, comorbid anxiety-depression and PTSD across all tumor types. This enhanced distress is clinically relevant even years after a cancer diagnosis. The lack of a concise definition of cancer survivorship likely contributes to the high heterogeneity among studies focusing on cancer survivors' psychological distress, which might hinder significant comparisons among studies.

Research perspectives

Developing generalized screening tools that examine psychological distress in cancer survivors for at least ten years after diagnosis could help to understand and address the psychological burdens of the survivors.

FOOTNOTES

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META-ANALYSIS

Effects of mindfulness-based intervention programs on sleep among people with common mental disorders: A systematic review and meta-analysis

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Abstract

BACKGROUND

Sleep problems are particularly prevalent in people with depression or anxiety disorder. Although mindfulness has been suggested as an important component in alleviating insomnia, no comprehensive review and meta-analysis has been conducted to evaluate the effects of different mindfulness-based intervention (MBI) programs on sleep among people with depression or anxiety disorder.

AIM

To compare the effects of different MBI programs on sleep among people with depression or anxiety disorder.

METHODS

Related publications in Embase, Medline, PubMed and PsycINFO databases were systematically searched from January 2010 to June 2020 for randomised controlled trials. Data were synthesized using a random-effects or a fixed-effects model to analyse the effects of various MBI programs on sleep problems among people with depression or anxiety disorder. The fixed-effects model was used when heterogeneity was negligible, and the random-effects model was used when heterogeneity was significant to calculate the standardised mean differences (SMDs) and 95% confidence intervals (CIs).

RESULTS

We identified 397 articles, of which 10 randomised controlled trials, involving a total of 541 participants, were included in the meta-analysis. Studies of internet mindfulness meditation intervention (IMMI), mindfulness meditation (MM), mindfulness-based cognitive therapy (MBCT), mindfulness-based stress reduction

(MBSR) and mindfulness-based touch therapy (MBTT) met the inclusion criteria. The greatest effect sizes are reported in favour of MBTT, with SMDs of -1.138 (95%CI: -1.937 to -0.340; P = 0.005), followed by -1.003 (95%CI: -1.645 to -0.360; P = 0.002) for MBCT. SMDs of -0.618 (95%CI: -0.980 to -0.257; P = 0.001) and -0.551 (95%CI: -0.842 to -0.260; P < 0.0001) were reported for IMMI and MBSR in the pooling trials, respectively. Significant effects on sleep problem improvement are shown in all reviewed MBI programs, except MM, for which the effect size was shown to be non-significant.

CONCLUSION

All MBI programs (MBTT, MBCT, IMMI and MBSR), except MM, are effective options to improve sleep problems among people with depression or anxiety disorder.

Key Words: Mindfulness-based intervention programs; Common mental disorders; Sleep; Systematic review; Meta-analysis

Core Tip: This meta-analysis provides evidence as to whether various kinds of mindfulness-based intervention programs can help improve sleep problems among people with common mental disorders. Our study indicated that integrative forms of mindfulness-based intervention programs (including mindfulness-based touch therapy, mindfulness-based cognitive therapy, internet mindfulness meditation intervention, and mindfulness-based stress reduction) have shown promising results. However, using mindfulness meditation solely should lead to insignificant effects.

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INTRODUCTION

Depression and anxiety disorder, also known as common mental disorders, are conditions that critically affect people's emotions, energy and ability to function. Approximately 1 in 5 adults were identified as meeting criteria for a common mental disorder over the past 12 mo, with the lifetime prevalence reported as 20.8% and 28.8% for depression and anxiety disorder, respectively[1,2]. Both depression and anxiety disorder are among the top 10 causes of disease burden worldwide[3], prompting the necessity to find ways for better treatment and planning of care.

Insomnia frequently co-occurs with both depression[4] and anxiety disorder[5]. Sleep problems, which include difficulty in falling asleep, early awakening, poor sleep quality, daytime sleepiness and poor adherence to the sleep-wake cycle pattern, are particularly prevalent among people with depression and anxiety disorder[6]. The relationships between insomnia and common mental disorders appear to be bidirectional[7]. Symptoms of anxiety and depression, such as worry and rumination, can contribute to insomnia. Alternatively, insomnia can also increase the likelihood of developing depression or anxiety disorder, possibly due to the psychological distress as well as hormonal and neurochemical disturbances caused by poor sleep[8,9]. Thus, interventions aiming at reducing symptoms of insomnia should provide benefit for the disorder *per se*[10].

Individuals may consider psychotherapy instead of pharmaceutical treatment, due to possible side effects and potential dependence on medication[11-13]. Cognitive behavioural therapy (CBT) has been substantially confirmed to be an effective psychosocial treatment in managing depression and anxiety [14,15]. In a meta-analysis of 1205 CBT trials for anxiety disorders, results indicated that CBT for anxiety has a moderate effect on sleep[16]. In terms of the treatment of both depression and insomnia, another study found that the addition of CBT for insomnia (known as CBT-I) to antidepressant medication treatment can lead to better treatment outcomes[17]. However, some reviews showed that the effect sizes of CBT for depression have steadily decreased since its inception four decades ago[18,19]. Therefore, merely employing CBT might not be sufficient for managing mood disorders and their corresponding sleep problems.

Due to the limitations of traditional treatments, many people who experience insomnia are willing to consider using complementary and alternative medicine (CAM) as an alternative therapeutic option,

including natural herbal products, acupuncture, or mind-body interventions, for example. A national health survey revealed that approximately 1.6 million adults in the United States have used CAM therapies to treat sleep problems[20]. Among different CAM therapies, the mind-body domains are by far the most commonly used[20]. Mindfulness-based interventions (MBIs), as a kind of CAM mind-body treatment with a focus on cultivating a sense of awareness, was originally developed to help people dealing with stress, anxiety, depression, or pain[21]. Mindfulness (Pali: *sati*) originated from Buddhism. As such, mindfulness can be defined as deliberately cultivating non-judgmental moment-to-moment awareness and experiences, through observing one's own mind in a detached manner[22]. Various formal and informal mindfulness activities, such as body scan and sitting meditation, are included within the MBIs. Through these practices, the technique of 'focusing on present moment' can be acquired based on approach, compassion and decentring[23]. The inquiry process, which assists participants in identifying their thoughts, emotions and behaviours, is also included in these programs to help participants respond with more flexibility and awareness[24].

Conventional MBI has standardised protocols, and typically incorporates three formal mindfulness practices, namely body scan, mindful movement and sitting meditation[23]. A traditional program called mindfulness-based stress reduction (MBSR), kicking off the development of the mindfulness-based program in the health care domain, was first introduced by Kabat-Zinn[22]. It is an 8-wk program using mindfulness meditation (MM) and mindfulness practice in everyday life to relieve stress. Since then, another well-researched program — mindfulness-based cognitive therapy (MBCT) — was developed with comparable structures[25]. It is also an 8-wk program, which includes mindfulness practice and psychoeducation about depression, promoting awareness, acceptance and adaptive reaction towards negative automatic thoughts[25]. Apart from preventing relapse in depression, MBCT is also used to treat patients with psychiatric conditions, like anxiety disorders and post-traumatic stress disorder (PTSD)[26,27].

Since the commencement of MBSR, various forms of mindfulness programs have evolved with different adaptations or modifications, such as the Mindfulness-Based Therapy for Insomnia (MBTI)[28], internet mindfulness meditation intervention (IMMI)[29], Mindfulness Awareness Program (MAP)[30], or mindfulness-based touch therapy (MBTT)[31]. Specifically, MBTI was developed for patients with insomnia. It integrates mindful meditation and behavioural therapy. By promoting awareness and adaptive response towards sleep disturbances, MBTI helps people with chronic insomnia with sleep restrictions and stimulus control[28]. IMMI was developed to offer mindfulness training anytime and anywhere by use of an Internet mode of delivery. IMMI includes six 1-h weekly sessions with 20 min of home-practice meditation between sessions[29]. MAP aims to teach participants principles of mindfulness, develop meditation practice and apply them in daily lives. MAP is mainly conducted in community settings, with a combination of lecture, hands-on practice, group feedback and discussion[30]. MBTT is an 8-wk program that combines components of MBSR and touch therapy. It was inspired by Ogden *et al*[32]'s model of hierarchical information processing, in which touch stimulus triggers sensorimotor reaction, which is then experienced as emotions and interpreted cognitively. Touch is believed to have healing effects on both the mind and body[31].

At present, various studies have been published for the different MBIs. However, the review type studies usually focus on the conventional programs, like MBSR or MBCT[33,34]. While there are different forms of emerging MBIs in recent years, it is essential to have a comprehensive evaluation on their clinical effectiveness. Moreover, the traditional MBI programs have usually targeted general physical and psychiatric conditions; later on, they were used in the management of various kinds of physical or psychosomatic conditions, and even insomnia problems[35]. Recent meta-analyses indicated that MBIs show promising effects on the reduction of sleep problems[36-39]. However, these meta-analyses focused on the general population only or on people with physical comorbidities, such as cancer and fibromyalgia. Therefore, systematic review and meta-analysis on the effectiveness of the various MBI programs for sleep problems in individuals with depression or anxiety disorders is implied.

The objective of this meta-analysis was to determine and compare the clinical importance of different MBI programs on sleep problems among individuals with common mental disorders. Based on our research, this meta-analysis is uniquely able to fill a crucial gap in the field.

MATERIALS AND METHODS

Literature search

Literature searches were performed according to the 2009 PRISMA Statement for systematic reviews, by two independent researchers (Lui D and Chan H). The search keywords of "mindfulness" and "mood or anxiety or depress*" and "sleep or insomnia" were used to ensure comprehensive coverage. Keyword searches were conducted in Embase, Medline (accessed through EBSCOhost), PubMed and PsycINFO (accessed through ProQuest) databases. Papers published between January 2010 and June 2020 were included. Publications were only restricted to English language and peer-reviewed.

Study eligibility

Titles and abstracts were screened, and full texts were selected for further review according to the following criteria. The inclusion criteria were as follows: (1) Experimental study with MBI; (2) Subjects selected for depression or anxiety disorder; (3) Sleep-related data taken at baseline and post-intervention; and (4) Randomised controlled trials (RCTs). The exclusion criteria were as follows: (1) Mixed intervention; or (2) Subjects with comorbidities other than depression or anxiety disorders. The selection criteria were confirmed according to the results of searching. The PRISMA flow diagram is shown in Figure 1.

Data extraction

An extraction form was used for each article to collect the following data: year of publication; subject setting; inclusion and exclusion criteria for participants; sample size for the experimental and control groups; participants' age and sex; intervention given; and outcome measures related to sleep quality. Relevant statistics and effect sizes were also extracted, if available.

Assessment on quality

Two reviewers (Lui D and Yip H), working independently, assessed the level of evidence (LoE) and appraisal stage for each of the articles using a standard quality assessment, namely the LoE[40] and revised cochrane risk-of-bias tool for randomised trials (RoB)[41] respectively. The LoE categorizes different experimental studies into different levels on a scale of I to V, with a smaller number indicating a higher LoE. The RoB was used to assess the risk of bias in the RCTs. A series of signalling questions were available in each of the five domains of assessment, and judgements were facilitated by an algorithm that maps responses to the signalling questions to a proposed judgement. Overall risk of bias of the individual study would be reported as "low risk of bias", "some concerns" or "high risk of bias". Disagreements between the two independent reviewers were resolved by a third reviewer through a consensus-based discussion.

Statistical analysis

Statistical analysis of the pooled results was carried out using the Comprehensive Meta-Analysis software version 3.0 (https://www.meta-analysis.com). In nine of the ten studies, standardised mean differences (SMDs) and 95% confidence intervals (CIs) were calculated using post-intervention differences between the mean of mindfulness-based programs and the mean of controls, divided by the pooled standard deviation. No real differences in variability among studies were assumed according to the Cochrane Handbook for Systematic Reviews of Interventions[42]. A global estimation of $r = 0.6$ was, therefore, used as the correlation coefficient between post-treatment scores. In the remaining study, Cohen's d was calculated using the two groups, *via* the one-way F-test using a practical meta-analysis effect size calculator[43]. When there was more than one group compared to the MBI group in the RCT, the non-intervention group was used as the control. The Q-statistic was used as the heterogeneity test, in which a statistically significant level of $P < 0.05$ indicated the variations in effect sizes were due to heterogeneity rather than sampling error. A random-effects model would be used when there was notable heterogeneity. Random-/fixed-effects models were used as the intervention effects are unlikely to be identical[44] given that there are significant variations in characteristics of each sample population. Publication bias was assessed by funnel plot, trim-and-fill and failsafe N. Unless otherwise specified, all statistical tests were two-sided with a significance level of 0.05.

RESULTS

Study selection

A total of 808 entries were identified through database searches, and 397 of them were screened after duplicates removed. After reading the abstract and title of the remaining 397, we removed 25 reviews, case reports, and protocols. Full versions were retrieved for 372 papers, after which they were reviewed by two independent researchers (Chan H and Sum K) and disagreements were resolved by a third reviewer (Lui D) on a consensus-based discussion. In total, 362 full articles were excluded for not meeting all the inclusion criteria. Finally, 10 eligible studies were selected for systematic review and meta-analysis (details shown in Figure 1).

Study characteristics

Ten studies met the inclusion criteria, overall reporting five different kinds of mindfulness-based programs, including IMMI, MM, MBCT, MBSR and MBTT. Table 1 shows the study characteristics of the 10 trials. The studies were conducted in the United States, Germany, Norway, Australia and Austria, within years that fell between 2010 and 2019. A total of 541 participants were included in the intervention groups and comparison groups. When there were multiple intervention groups, we chose the mindfulness-based programs as the major intervention groups[45-47].

Table 1 Characteristics of studies

Ref.	Country	Sample	Age range (mean)	Women, *n* (%)	Randomisation	Intervention group (comparison group)	Intervention duration	Group size for effect size calculation, *n*	Drop-out rate[1] (%)	Outcome measure for sleep
Wahbeh [29], 2018	United States	Older adult with depression symptoms	55-80 (64.8)	21 (81)	R	IMMI (waitlist control)	6 wk	I = 26 C = 24	20.00	Sleep disturbance, ISI
Boettcher *et al*[50], 2014	Germany	Community dwellers with anxiety disorders	18+ (37)	34 (75.6)	R	IMMI (discussion forum control group)	8 wk	I = 45 C = 46	7.69	ISI
Wahbeh *et al*[47], 2016	United States	Combat veterans with post-traumatic stress disorder	25-65 (I = 53.3; C = 53.0)	2 (7)	R	MM (sitting quietly)	6 wk	I = 27 C = 25	0	PSQI
Britton *et al*[49], 2012	United States	Antidepressant medication users with sleep complaints	24-61 (47.0)	21 (80.8)	R	MBCT (control)	8 wk	I = 14 C = 10	7.69	TIB, TST, SE, SOL, WASO, TWT, Stage 1, SWS, Quality
Vøllestad *et al*[51], 2011	Norway	Community dwellers with anxiety disorders	18-65 (42.5)	26 (66.7)	R	MBSR (waitlist control)	8 wk	I = 39 C = 37	14	BIS
Britton *et al*[48], 2010	United States	Community dwellers with partially remitted depression	33-64 (45.4)	9 (69.2)	R	MBCT (control)	8 wk	I = 13 C = 8	19.23	TIB, TST, SE, SOL, WASO, NWAK, Arousals, Stage 1, SWS, Quality
Hoge *et al* [52], 2013	United States	Referral/community dwellers with generalized anxiety disorder	18+ (I = 41; C = 37)	23 (47.9)	R	MBSR (stress management education)	8 wk	I = 48 C = 45	4.30	Sleep quality, PSQI
Horenstein *et al*[45], 2019	United States	Adults with social anxiety disorder	18+ (32.7)	Not specified	R	MBSR (control)	12 wk	I = 36 C = 36	15.28	Sleep quality, PSQI
Pinniger *et al*[46], 2013	Australia	Adults with self-reported feelings of stress, anxiety, and/or depression	18-68 (39.5)	10 (90.9)	R	MM (waitlist control)	8 wk	I = 11 C = 23	30.60	Sleeping difficulty/insomnia, ISI
Stötter *et al* [31], 2013	Austria	Patients of the psychiatric hospital of Hall in Tirol	18+ (I = 42.8; C = 41.4)	11 (68.75)	R	MBTT (control)	8 wk	I = 14 C = 14	0	Sleep-onset disorder, Sleep maintenance disorders, Terminal sleep disorders, HDRS

[1]When there are multiple intervention groups, the drop-out rate is based on the number of participants in Mindfulness-Based Program and comparison group only. BIS: Bergen insomnia scale; C: Comparison group; I: Intervention; HDRS: Hamilton's depression rating scale; IMMI: Internet mindfulness meditation intervention; MBCT: Mindfulness-based cognitive therapy; MBSR: Mindfulness-based stress reduction; MBTT: Mindfulness-based touch therapy; NWAK: Number of awakenings; ISI: Insomnia severity index therapy; MM: Mindfulness meditation; PSQI: Pittsburgh sleep quality index; R: Randomised; SE: Sleep efficiency; SOL: Sleep onset latency; Stage 1: Sleep onset was defined by the first epoch of any stage of sleep; SWS: Short-wave sleep; TIB: Time in bed; TST: Total sleep time; TWT: Total wake time; WASO: Wake after sleep onset.

Across studies, participants had a range of mean age between 32.7 and 64.8 years. Seven out of ten (70%) of the studies had a majority of female participants. Four out of ten studies (40%) focused on community dwellers with anxiety and/or major depressive disorder. One study included participants of veterans with PTSD. Six out of ten studies reported significant improvement in sleep quality as measured by insomnia severity index (ISI), Pittsburgh sleep quality index (PSQI), Bergen insomnia scale (referred to as BIS), Hamilton depression rating scale (HDRS) and sleep diaries, provided that the *P* value of the experiment was lower than 0.05. All of the studies were RCTs. The duration of the intervention ranged from 6 wk to 12 wk and delivered over 6 to 12 sessions. Details of intervention techniques and selected outcome measures of each study are provided in Table 2.

Table 2 Interventions' technique, components and selected outcome measures for effect size calculation

Mindfulness-based program	Intervention components		Selected outcome measures for effect size calculation	Ref.
	Intervention group	Comparison group		
IMMI	DI + MM + MPS	WL	ISI	Wahbeh[29], 2018
	ME + psychoeducation	DF	ISI	Boettcher *et al*[50], 2014
MM	BS	SB	PSQI	Wahbeh *et al*[47], 2016
	BS	BS + SB	PSQI	Wahbeh *et al*[47], 2016
	BS	SQ	PSQI	Wahbeh *et al*[47], 2016
	BS + MB + MW + music meditation	WL	ISI	Pinniger *et al*[46], 2013
MBCT	MA + HW (Guided audio CD)	Control	Sleep diary	Britton *et al*[48], 2010
	MA (MB + MS + MW + lying + other simple movement) + HW (MM using audio CD + worksheet)	Control	Sleep diary	Britton *et al*[49], 2012
MBSR	BS + SM + MB + AR + DI + ME + MMV + HW	WL	Bergen insomnia scale	Vøllestad *et al*[51], 2011
	BS+ BA+ gentle Hatha Yoga	SME	PSQI	Hoge *et al*[52], 2013
	BS + SM + MS + MPS	WL	PSQI	Horenstein *et al*[45], 2019
MBTT	BA + touch + HW + counselling	BMT	HDRS	Stötter *et al*[31], 2013

AR: Adaptive response; BA: Bodily awareness; BMT: Basic medicinal therapy; BS: Body scan; DF: Discussion forum; DI: Didactic instruction; HDRS: Hamilton depression rating scale; HW: Homework; IMMI: Internet mindfulness meditation intervention; ISI: Insomnia severity index; MA: Mindfulness awareness; MB: Mindful breathing; ME: Mindfulness exercise; MBCT: Mindfulness based cognitive therapy; MBSR: Mindfulness based stress reduction; MBTT: Mindfulness based touch therapy; MM: Mindfulness meditation; MMV: Mindful movement; MPS: Mindfulness problem-solving; MS: Mindful stretching; MW: Mindful walking; PSQI: Pittsburgh sleep quality index; SB: Slow breathing; SM: Sitting meditation; SME: Stress management education; SQ: Sitting quietly; WL: Waitlist control.

Assessment of quality

Results from quality assessments are presented in Tables 3 and 4. All studies were RCTs. All trials had adequate sequence generation, among which five (50%) indicated a concealed allocation[49-51]. As for blinding, two trials adopted double-blind design[48,49], one trial used single-blind design[31] and two used blind evaluators[47,52]. The drop-out rates of the trials ranged from 0% to 30.6%, as shown in Table 1. Of the 10 trials, 3 had low drop-out rates (≤ 5%)[31,47,52] and two had high drop-out rates (≥ 20%)[29,46]. The overall LoE was level II (n = 10), showing that the papers under current review were of high LoE. The overall RoBs were as follows: low (n = 2); some concerns (n = 6); and high (n = 2). The majority of papers showed some concerns of risk of bias, mainly due to bias in the measurement of outcome.

Analysis of overall effect

This meta-analysis focused on examining the effect at the end point of different mindfulness-based programs, including IMMI, MM, MBCT, MBSR and MBTT, due to variations in follow-up periods and absence of reported follow-up effects in several studies. The overall effect analysed was based on the comparison between different mindfulness-based programs and comparison groups, including discussion forum, waitlist control, slow breathing, stress management education, sitting quietly and basic medicinal therapy. Self-rated outcome measurements were reported in the 10 RCTs assessed, including PSQI, ISI, sleep quality of sleep diary, and sleep maintenance of HDRS. The overall scores of sleep quality were reported in PSQI, ISI, BIS and sleep diaries. On the other hand, there was no overall score on sleep quality presented in HDRS. The component of sleep maintenance in HDRS was, therefore, selected. Sleep maintenance was selected instead of sleep onset and sleep termination, as the level of sleep maintenance better predicts perceived sleep quality[53]. Other outcome measurements which are not self-rated, including sleep onset latency, total sleep time and wake after sleep onset, were not reported in this meta-analysis.

The mean effect sizes on sleep problem improvement of different mindfulness-based programs, as compared with control groups, are provided in Table 5. The forest plot in Figure 2 shows the effect sizes and 95%CIs of the 10 studies assessed. The meta-analysis reveals a moderate pooled effect size (g = -0.527, 95%CI: -0.701 to -0.353) in favor of MBI program. Significant effects on sleep problem improvement were shown in four out of five of the different mindfulness-based programs under

Table 3 Research design and level of evidence

Ref.	Research design	Level of evidence
Wahbeh[29], 2018	RCT, crossover design	II
Boettcher *et al*[50], 2014	RCT, crossover design	II
Wahbeh *et al*[47], 2016	RCT, multi-group pre-/post-test design	II
Britton *et al*[49], 2012	RCT, pre-/post-test control group design	II
Vøllestad *et al*[51], 2011	RCT, crossover design	II
Britton *et al*[48], 2010	RCT, pre-/post-test control group design	II
Hoge *et al*[52], 2013	RCT, two group pre-/post-test design	II
Horenstein *et al*[45], 2019	RCT, multi-group pre-/post-test design	II
Pinniger *et al*[46], 2013	RCT, multi-group pre-/post-test design	II
Stötter *et al*[31], 2013	RCT, pre-/post-test control group design	II

RCT: Randomised controlled trial.

Table 4 Risk of bias in the studies

Ref.	Randomisation process	Deviation from intended intervention	Missing outcome data	Measurement of outcome	Selection of the reported results	Overall
Wahbeh[29], 2018	Low risk	Low risk	Some concerns	Some concerns	Low risk	High
Boettcher *et al*[50], 2014	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Wahbeh *et al*[47], 2016	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Britton *et al*[49], 2012	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Vøllestad *et al*[51], 2011	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Britton *et al*[48], 2010	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Hoge *et al*[52], 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low
Horenstein *et al*[45], 2019	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Pinniger *et al*[46], 2013	Low risk	High risk	Some concerns	Low risk	Low risk	High
Stötter *et al*[31], 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low

review, namely MBTT, MBCT, IMMI and MBSR (reflecting descending order of effect sizes). The greatest effect sizes were reported in favour of MBTT, with SMDs of -1.138 (95%CI: -1.937 to -0.340; P = 0.005), followed by -1.003 (95%CI: -1.645 to -0.360; P = 0.002) for MBCT. SMDs of -0.618 (95%CI: -0.980 to -0.257; P = 0.001) and -0.551 (95%CI: -0.842 to -0.260; P < 0.0001) were reported for IMMI and MBSR in the pooling trials, respectively. However, among the five kinds of mindfulness-based programs under review, the mean effect size for MM on sleep was non-significant, with SMD of -0.264 (95%CI: -0.699 to 0.172; P = 0.236).

Heterogeneity test and publication bias

Table 5 shows that all the heterogeneities (Q) were non-significant across the different MBI programs. The non-significant Q-statistics might suggest that the variation in the effect sizes across the studies was simply due to low power but not the study characteristics. Three sets of asymmetry tests — namely, funnel plots of precision, trim-and-fill and failsafe N — were used to estimate the publication bias in each study. Symmetrical distribution of the combined effect size revealed the absence of publication bias

Table 5 Overall effects of different interventions

Ref.	Mindfulness-based program	*k*	Subjects, *n*	SMD (95%CI)	*P* value	Overall SMD (95%CI)	Overall *P* value	*Q*
Wahbeh[29], 2018	IMMI	2	124	-0.881 (-1.531 to -0.231)	0.008	-0.618 (-0.980 to -0.257)	0.001	0.912 (*P* = 0.34)
Boettcher *et al*[50], 2014				-0.500 (-0.935 to -0.066)	0.024			
Wahbeh *et al*[47], 2016	MM	2	86	-0.267 (-0.814 to 0.279)	0.337	-0.264 (-0.699 to 0.172)	0.236	0.001 (*P* = 0.981)
Pinniger *et al*[46], 2013				-0.257 (-0.978 to 0.464)	0.485			
Britton *et al*[48], 2010	MBCT	2	43	-1.073 (-1.953 to -0.192)	0.017	-1.003 (-1.645 to -0.360)	0.002	0.052 (*P* = 0.82)
Britton *et al*[49], 2012				-0.923 (-1.862 to 0.016)	0.054			
Hoge *et al*[52], 2013	MBSR	3	187	-0.449 (-0.942 to 0.043)	0.074	-0.551 (-0.842 to -0.260)	< 0.0001	0.332 (*P* = 0.847)
Horenstein *et al*[45], 2019				-0.555 (-1.056 to -0.053)	0.03			
Vøllestad *et al*[51], 2011				-0.660 (-1.178 to -0.141)	0.013			
Stötter *et al*[31], 2013	MBTT	1	28	-1.138 (-1.937 to -0.340)	0.005	-1.138 (-1.937 to -0.340)	0.005	0 (*P* = 1)

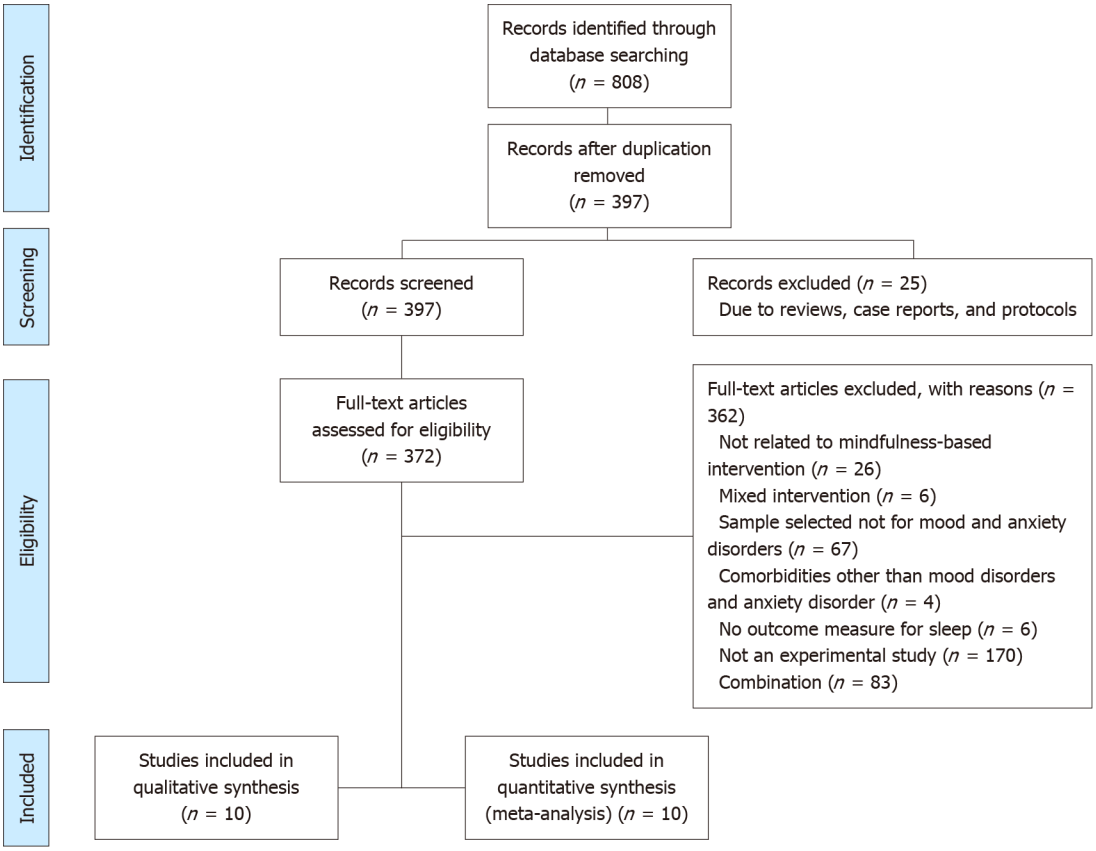
CI: Confidence interval; IMMI: Internet mindfulness meditation intervention; MBCT: Mindfulness-based cognitive therapy; MBSR: Mindfulness-based stress reduction; MBTT: Mindfulness-based touch therapy; MM: Mindfulness meditation; SMD: Standardised mean difference.

upon visual inspection of the funnel plots (Figure 3). To further examine the funnel plot symmetry, Duval and Tweedie's trim-and-fill procedure was used. No significant adjustment was needed and no study was trimmed due to the absence of unmatched observations from the funnel plots. Failsafe N analyses demonstrated that 96 missing studies with a zero effect size have to be added to reduce the significant overall effect size to statistically non-significant levels.

DISCUSSION

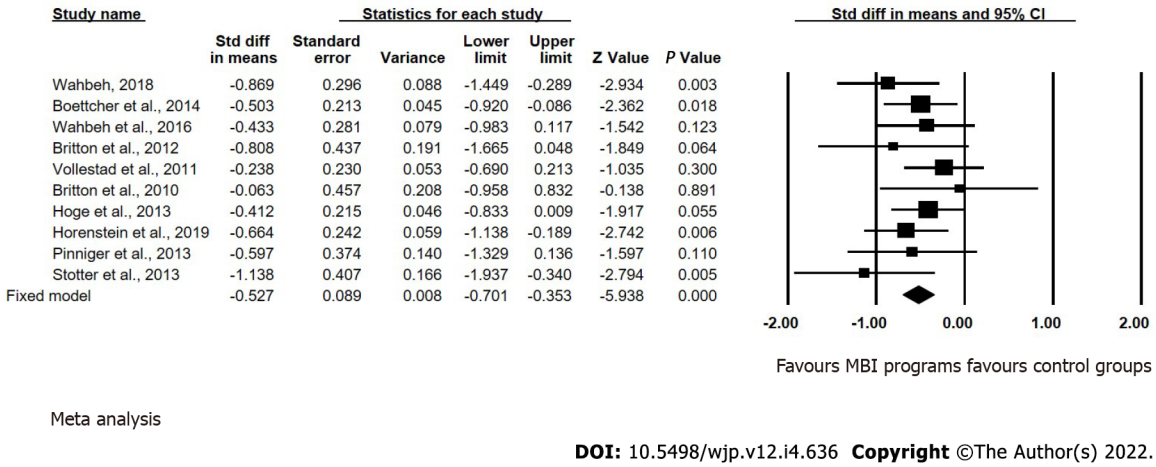
This meta-analysis showed that MBTT imparts the largest effect on sleep problems among the five different kinds of mindfulness-based programs under review, followed by MBCT, IMMI and MBSR. According to Cohen[54]'s thresholds for interpreting effect size, SMDs smaller than 0.20 would be regarded as small effect size, 0.50 as medium, 0.80 as large and 1.30 as very large. However, it is important to point out that Cohen defined the medium effect size based on his literature review using the *Journal of Abnormal and Social Psychology* during the 1960s. These small, medium, and large effect sizes are, thus, specific to a particular domain (abnormal and social psychology) and as such these cut-off points should not be treated as absolute or universal. By Cohen's convention, MBTT and MBCT have large effect sizes. IMMI and MBSR have medium effect sizes, and MM has a small effect size. It should be noted that, despite the large effect size of MBTT on sleep, only one study contributed to this result, while the results of the remaining four different kinds of mindfulness-based programs were supported by at least two or more studies. In addition, the effect of MM on sleep did not reach a significant level, despite having a small effect size. This may be explained by the unexplored improvements in sleep problems in the comparison group, leading to the comparatively non-significant effect of MM. Although previous findings suggested that MM is an effective treatment for insomnia[37], its effect on sleep for people with depression and anxiety disorder remains questionable, as shown in this meta-analysis.

As such, MBTI has been commonly used to treat patients with chronic insomnia or sleep problems [35]. However, many studies involving MBTI[28,55] did not target people with depression or anxiety disorder, so MBTI was not selected in the current meta-analysis (according to the inclusion criteria). When further scrutinized, the goals of MBTI usually aim at promoting the adaptive response towards the emotional distress caused by sleep disturbances and daytime fatigue among people with chronic insomnia. However, the present review study revealed that those MBI programs which can improve sleep problems among people with depression or anxiety disorder may have additional characteristics. More specifically, those MBI programs under review were found to ameliorate both the mood and sleep



DOI: 10.5498/wjp.v12.i4.636

Figure 1 PRISMA flow diagram of the study.



DOI: 10.5498/wjp.v12.i4.636

Figure 2 Forest plot of effect sizes. MBI: Mindfulness-based intervention; CI: Confidence interval.

problems concurrently. In other words, these MBI programs could target both the antecedents and consequences of sleep problems for people with common mental disorders.

MBTT[31] was found to have the largest effect on sleep problems, according to the meta-analysis. MBTT, which is based on mindfulness practice and various forms of massage and bodywork, could improve sleep by restoring interception and sensorimotor processing of individuals with depression and anxiety disorder. Regarding the effect of touch *per se*, the rhythmic and gentle massage produced a direct bodily and sensory experience[31]. This resulted in an antidepressant effect mediated by restoration of the impaired interoceptive functioning, which is associated with depression and anxiety [56,57], through stimulation of specific mechanoreceptors[58]. Adding to the independent effect of touch, a possible explanation for the synergistic effects of combining mindfulness practice and therapeutic touch is the model of hierarchical information processing, which suggested that mindfulness-based touch intervention gave rise to the integration of sensorimotor bodily experience

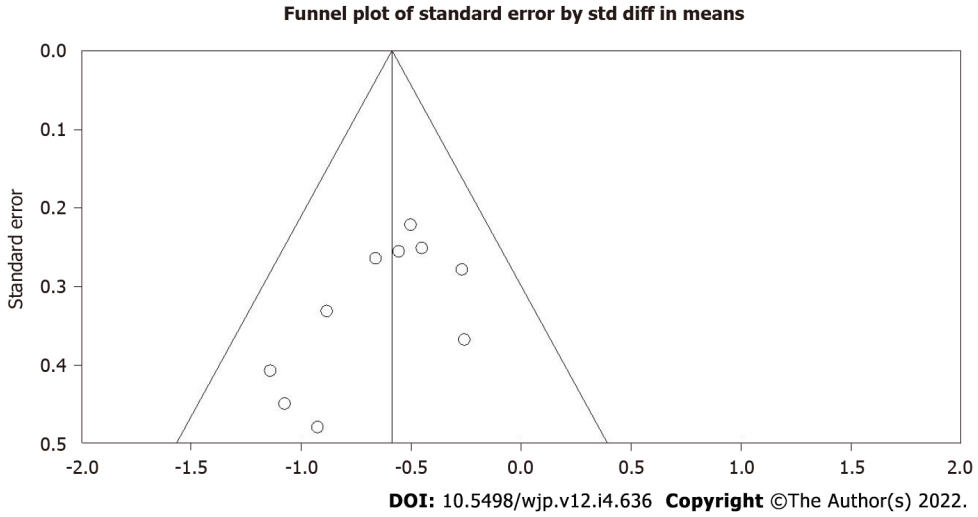


Figure 3 Funnel plot of standard error by standard difference in means.

with mindful cognitive self-awareness[32]. In line with this explanation, a cortical plasticity model suggested that the sensory reorganization sprung from touch therapy was a mechanism for pain remediation[59]. Similarly, considering a previous study documenting the relationship between sensory processing and sleep quality[60], it is plausible that improving sensory processing through a mindfulness-orientated touch approach could, in turn, ameliorate sleep disturbance in people with depression or anxiety disorder.

Besides, we also found that MBCT[48,49] can help improve sleep problems among people with depression or anxiety disorder, with large effect sizes. In addition to traditional mindfulness skills, MBCT incorporates cognitive behavioural skills which can enhance the effectiveness in coping with depressive mood and sleep problems. Despite the interrelated nature of depression and insomnia, it is theoretically debatable whether insomnia should be treated as a distinct diagnosis or a symptom of mood disorders[61]. Considering the complexity of insomnia, Shallcross *et al*[62] proposed a theoretical model to summarize the utility of MBCT in treating insomnia, suggesting that there are three treatment components (*i.e.*, acceptance, attention control and experiential awareness) with different therapeutic functions across the integrated process model of insomnia. It is worth noting that the model of insomnia is in line with symptoms of people with depression. For example, rumination is associated with both depressive mood and sleep quality[63] and upregulated arousal is linked to sleep problems (*e.g.*, longer sleep latency) in people with depressive syndromes[64,65]. The review studies suggested that MBCT can ameliorate the sleep disturbance of people who have achieved partial remission of depression (both with and without taking an anti-depressant) as well as significant mood improvement. It is possible that MBCT is not only a promising program for depression or insomnia alone, but also for improving sleep problems in people with depression. In addition, recent research has indicated that acceptance lessened the positive relation between awareness and sleep disturbance, with reduced stress level identified as a mediator[66]. This mechanism is consistent with the Monitor and Acceptance Theory[67], which proposes that awareness and acceptance may jointly improve emotional regulation, including that of stress. In this sense, the effectiveness of MBCT to reduce stress[68,69] can partially explain the potential utility of MBCT in improving sleep outcomes.

Therefore, solely utilizing MM[46,47] may not be robust enough to improve sleep problems among people with depression or anxiety disorder, as indicated by the insignificant effect size shown in this study. No wonder recent meta-analyses[70,71] supported that MM is effective in reducing symptoms such as rumination among people with depression or anxiety disorder, but the sleeping problem might be improved in the short-term only. As a bidirectional relationship has been revealed between sleep disturbance and common mental disorders[7], it seems that a more integrated approach should be considered in order to enhance robustness of the intervention effects. For instance, the addition of a touch approach[31], cognitive component[50] or health qigong[72] should help in promoting the effectiveness of mindfulness practice, as applied in different clinical populations. Thus, the evolution of various kinds of integrated MBI programs should mark the necessity for meeting the increasing demand of various physical and mental health problems.

Our analysis showed that the majority of studies were coded as having some concerns by RoB. Most concerns arise from measurement of outcome, as most sleep measurements, such as PSQI, ISI and sleep diary, rely on self-report by the patients. With the awareness of the treatment received, the non-blind allocation should lead to increased risk of bias. In addition, improvements in sleep cannot be merely assessed by objective tools like polysomnography but will also still rely on self-rated assessment tools. Thus, there is a possibility that some studies of good quality are not coded as low RoB due to the strict

restrictions in outcome measurement tools, as stated in the RoB tool used in the current study. The studies included in this meta-analysis involved diverse sample populations in various age groups and with different emotional disorders, including mood disorders, anxiety disorders and PTSD. However, the heterogeneities were not significant, despite the variations in study characteristics. This may be explained by the high similarity in outcome measurement tools, among which PSQI, ISI and sleep diary were widely used to assess sleep outcome in the studies. Moreover, many of the studies under review had similar study protocols, and some were even conducted by the same group of researchers. The non-significance in heterogeneity may also be attributed to the low power of the studies. Nevertheless, moderator analysis can be considered in the future for possible effects of the potential moderators.

Although the present meta-analysis suggests considerable clinical benefits of MBTT, MBCT, IMMI and MBSR on sleep among people with depression or anxiety disorder, the findings should be interpreted with caution. It should be noted that this meta-analysis has been primarily concerned with its limited power. A limited number of clinical trials on MBI programs are available in the literature databases, and many of the studies targeted populations with physical complications or other comorbidities. The result was that a relatively small number of trials met inclusion criteria. For example, there was only one study regarding MBTT that could be included. Thus, the effect of MBTT in our meta-analysis was solely determined by one study. The ability of funnel plot to detect publication bias was also restrained by the few number of trials included in our meta-analysis. Thus, there is a need to include larger clinical trials in the future to increase the study power. This analysis has concentrated on studying different kinds of MBI programs but not the specific components in the programs. It caused our study to have low generalizability compared to all the other protocols of the studied programs, because variations exist under the same program between different studies. For instance, gentle Hatha Yoga was included in one study of MBSR[52] but not in other trials[45,51]. Therefore, the effects of the MBI programs in this study are composed of various but nonspecific components. Further studies on specific intervention components, such as body scan, mindful walking, bodily awareness and mindful breathing are required. A further potential limitation of this review stems from the fact that the outcome measures of sleep focus on the subjective measurements only. The discrepancies in sleep measurement may have complicated the comparison. It is suggested that more objective and uniform measurement tools for sleep should be used in future studies in this field to facilitate a larger sample size and power in prospective systematic reviews and meta-analyses. For instance, polysomnography and electrocardiogram use scientific technology to investigate some objective components of sleep and can be considered[49,73]. These could provide more objective evidence than self-rated scales. Lastly, the lack of Asian studies means that we cannot be certain that the findings can be generalized to an Asian population. Studies included in the current review were carried out only in the United States, Germany, Norway, Australia and Austria. More clinical trials in Asian countries are encouraged to increase generalizability of findings from future studies. It is also suggested that a more specific age group could be targeted to study the effect of MBIs on different age groups, like elderly and adolescent.

Despite these limitations, this review study adds to the literature by investigating different kinds of MBI programs on sleep problem among people with common mental disorders. The comprehensive inclusion and exclusion criteria contribute to the uniqueness of this meta-analysis. Studies that included subjects with comorbidities and with mixed intervention were excluded and, at the same time, a wide variety of MBI programs were included. The criteria allowed this meta-analysis to focus more on the effect of different MBI programs in order to fill in a lacuna in the research. Additionally, this meta-analysis has the following strengths. First, it followed the guidelines of the Cochrane Collaboration, which provided a standard process of analysis. The PRISMA Statement was also adopted to support the integrity of its systematic review process. Second, only RCTs were included in this analysis. All the studies analysed had high LoEs and most of them had low to moderate risk of bias. Bias is reduced by study design of adequate concealed allocation and blinding. The high quality of study design of the 10 included studies assured the reliability and validity of their results. Thus, this meta-analysis truly reflects the effect of different MBI programs. Third, all the studies analysed were conducted in the last decade. Since the first introduction of MBCT and MBSR by Kabat-Zinn[22], many innovative forms of MBI have been developed, as mentioned in the introduction. The clinical interest towards MBI has continued throughout the years. The meta-analysis in this paper included studies conducted in 2011-2019, providing up-to-date information about the effect of different MBI programs on sleep among people with depression or anxiety disorders. The meta-analysis in this paper also focused on a specific client group and, as such, was able to provide an updated overview of comparison with traditional MBI and the newly developed programs.

CONCLUSION

The findings of our comprehensive systematic review and meta-analysis provide preliminary evidence that MBTT, MBCT, IMMI and MBSR are effective options to improve sleep among people with depression and anxiety disorder. MM, which has confirmed to be effective in improving sleep in people with chronic insomnia, may not be effective in our targeted population. Taken together, these results

might provide a first step toward designing more integrated effective interventions for this specified clinical population who are suffering from sleep problems. We are hopeful that the findings of our research will inform health practitioners and other researchers on the extent of effectiveness of the different, latest and integrated MBI programs.

ARTICLE HIGHLIGHTS

Research background

Sleep problems are particularly prevalent in people with depression or anxiety disorder. Although mindfulness has been suggested as an important component in alleviating insomnia, no comprehensive review and meta-analysis has been conducted to evaluate the effects of different kinds of mindfulness-based intervention (MBI) programs on sleep among people with depression or anxiety disorder.

Research motivation

The present study aimed to assess randomised controlled trials of various types of MBI programs for improving sleep problems in people with common mental disorders.

Research objectives

The main objective was to evaluate and update evidence of effectiveness of the different, latest and integrated MBI programs.

Research methods

We performed a systematic literature search on Embase, Medline, PubMed and PsycINFO databases from January 2010 to June 2020 for randomised controlled trials. Data were synthesized using a random-effects or a fixed-effects model to analyse the effects of various MBI programs on sleep problems among people with depression or anxiety disorder. The fixed-effects model was used when heterogeneity was negligible, and the random-effects model was used when heterogeneity was significant to calculate the standardised mean differences (SMDs) and 95% confidence intervals (CIs).

Research results

We identified 397 articles, of which 10 randomised controlled trials, involving a total of 541 participants, were included in the meta-analysis. Studies of internet mindfulness meditation intervention (IMMI), mindfulness meditation (MM), mindfulness-based cognitive therapy (MBCT), mindfulness-based stress reduction (MBSR) and mindfulness-based touch therapy (MBTT) met the inclusion criteria. The greatest effect sizes are reported in favour of MBTT, with SMDs of -1.138 (95%CI: -1.937 to -0.340; P = 0.005), followed by -1.003 (95%CI: -1.645 to -0.360; P = 0.002) for MBCT. SMDs of -0.618 (95%CI: -0.980 to -0.257; P = 0.001) and -0.551 (95%CI: -0.842 to -0.260; P = 0.000) were reported for IMMI and MBSR in the pooling trials, respectively. Significant effects on sleep problem improvement are shown in all reviewed MBI programs, except MM, in which its effect size was shown to be non-significant.

Research conclusions

This review presents a comprehensive meta-analysis of various forms of MBI programs on helping sleep problems among people with common mental disorders. We found that all MBI programs (in terms of MBTT, MBCT, IMMI and MBSR), except MM, are effective options to improve sleep problems among people with depression or anxiety disorder.

Research perspectives

The current meta-analysis suggests that solely utilizing MM may not be robust enough to improve sleep problems among people with depression or anxiety disorder. As a bidirectional relationship was revealed between sleep disturbance and common mental disorders, it seems that a more integrated approach should be considered in order to enhance robustness of the intervention effects.

FOOTNOTES

Author contributions: Chan SHW conceived and guided the study; Lui D and Chan H carried out the literature searches; Chan H and Sum K extracted the data; Lui D and Yip H assessed the study quality; Yu CH, Lui D and Sum K performed the statistical analyses; Chan SHW, Lui D, Cheung A and Yip H wrote and revised the paper.

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