

Appropriate Commencement, Perpetuation, and Abstinence of Commonly Subsumed SSRIs, SNRIs, and TCAs Imperative in the Management of Panic Disorder- An overview

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ABSTRACT

Panic attacks are unjustified anxieties and worries accompanied by a racing heart, fast breathing, and sweating. Some people acquire panic disorder, which is a form of anxiety disorder characterised by recurring panic attacks, as a result of their fear of these episodes or any other underlying pathophysiology. Heredity, thyroid gland dysfunction, low blood sugar levels, depression, phobias, and post-traumatic events among others, have all been linked to the major causes of panic disorder. Although norepinephrine, serotonin, dopamine, and gamma-aminobutyric acid (GABA) neurotransmitter systems are considered to play a crucial role in all of the cases. This condition is caused by malfunctions in their release, uptake, extracellular build-up, and lack of central control. This is justified by the fact that psychoactive medicines that alter these neurotransmitter systems have a significant impact on the pathophysiology of this disorder. Antidepressants including selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and benzodiazepines are currently recommended as first-line treatment for this illness. The most crucial elements to consider while administering these antidepressants are optimal medication start-up, correct dosage, proper length and consistency of usage, and finally progressive discontinuation. Unfortunately, physicians and patients commonly overlook all of these factors, resulting in recurrent occurrences of this disease caused by inadequate neurotransmitter activation. At first, these drugs create an exaggeration of symptoms, which is followed by the onset of withdrawal syndrome when the medication is stopped. These drugs require a certain delivery pattern as well as a set period in order to produce stable correlation neurochemistry. As a result, patients must be aware of the precise start, duration, and termination of these drugs prior to their administration.

Keywords: Panic disorder; Panic attack; Antidepressants; Neurotransmitters; Withdrawal syndrome; CBT

INTRODUCTION

In the realm of psychiatry, panic disorder and panic attacks are two of the most common issues that patients experience. In spite of the fact that panic disorder is characterized by frequent and abrupt panic episodes with a frequency of 2-5 per day, it is separate from panic attacks. Panic attacks, particularly those linked to panic disorder, strike without warning, often without a clear reason. Panic attacks are rarely life-threatening, but if not managed properly, they can lead to a variety of illnesses. Panic attacks are defined by the Diagnostic and Statistical Manual of Mental Health Disorders (DSM) as a rapid surge of extreme fear or discomfort that peaks within minutes [1]. A panic attack is defined by three or more physical symptoms, which may include palpitations, sweating with chills or heat sensations, shaking (trembling), choking feelings, light-headedness or faintness, shortness of breath (suffocation), nausea/anorexia, abdominal distress, chest discomfort, dizziness, unsteadiness, losing control over self or going insane, depersonalization (being detached from oneself), paresthesias (numbness or tingling), derealization (feelings of unreality), and dread of dying [2]. Although there is seldom a specific reason for a panic attack, a rise in anxiety level appears to be a crucial trigger for someone with panic disorder. Panic attacks, on the other hand, can occur in the context of other anxiety, mood, psychotic, and substance-abusing illnesses such as phobia, post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), or depression [3]. Panic disorder, whether with or without agoraphobia, is one of the most common and dangerous anxiety disorders in the general population in the Western world, with a yearly prevalence of 2-3% in Europe. Another 1% of the population has agoraphobia without panic attacks [4]. Patients afflicted with this disorder need a lot of medical aid, find it hard to socialize and perform their daily tasks, and have a deteriorated overall quality of life. However short-term psychological therapy with or without medications can help the patients to recover from this disorder completely. A set of tools and guidelines are incorporated by general psychiatric practitioners to carry out such operations. Regarding the evidence-based studies and procedures on agoraphobia and panic disorder, the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria is incorporated. However, many psychiatrists and counselors incorporate the International Classification of Diseases (ICD-10) criteria which states that the "essential feature is repeated episodes of severe anxiety (panic), which are not restricted to any one scenario or set of circumstances and are hence unpredictable." [2, 5].

ONSET AND TRIGGERS OF PANIC ATTACKS

The major causes of panic disorder have been interconnected to inherited conditions, thyroid gland dysfunction, low blood sugar levels, unprecedented withdrawal of some drugs or alcohol, phobias, depression, significant life upheavals, fail to achieve anticipations, traumatic situations, and exorbitant use of stimulants such as caffeine and cocaine [6]. Panic attacks are classified into the following types relying on the link between the incidence of the episode and the existence or exclusion of ambient inducers:

- ❖ Unproven or unexpected episodes are the most prevalent form of a panic attack in panic disorder, where the onset of a panic attack is unrelated to a contextual trigger and may appear spontaneously as a lightning strike
- ❖ Situational-triggered panic episodes almost typically appear shortly after being exposed to or expecting a trigger situation.
- ❖ Contextual primed panic episodes are more probable to happen when the triggering situation is given but are not inextricably related to it and do not have to happen right away.

Panic episodes can happen in a variety of contexts, but they become practically chronic in panic disorder with agoraphobia [7]. An individual with panic disorder, for example, may wake up with a clean mentality, but after a few minutes, he begins to sense something is wrong, and something in the body, such as a pounding chest, a highly burdened mind filled with turbulence, or anorexia, may occur. After a while, this ailment reaches a pinnacle and leads to a panic attack. It is more likely to occur, however, when a person learns of a neighbour's or friend's premature death due to ailments such as heart attack or cancer. The victim began to think that he is suffering from symptoms of a disease that actually did not exist (hypochondria), and he began to lose control of himself. In the event of a panic attack connected with agoraphobia, there is a persistent fear of being in locations or circumstances where getting out is challenging or embarrassing, or where assistance may not be accessible. If aversion is restricted to a single scenario, it is referred to as a specific phobia, and if it is limited to social situations, it is referred to as a social phobia. The sufferer deeming a risk of having a panic attack avoid the events or go through colossal stress and effort to handle a particular situation [3, 8].

PATHOPHYSIOLOGY

A panic attack is defined by the American Psychiatric Association as a period of intense worry or discomfort during which three or more of the following symptoms appear abruptly and peak within a few minutes [9, 10]:

- Palpitations (accelerated heart rate)
- Shaking or trembling
- Fear of going crazy or losing control
- Sweating and feeling hot flashes in the pelvic region or Chills
- Smothering or sensations of shortness of breath
- Chest distress or discomfort
- Feeling of Paresthesia
- Nausea, anorexia, or abdominal distress
- Feelings of vertigo, dizziness, lightheaded, unsteadiness.
- Depersonalisation (being detached from oneself) and Derealisation (feelings of unreality)
- Dread of dying

At this moment, the exact etiology of panic disorder is unknown. According to biological theories, the primary etiology of this disorder is linked to hereditary predisposition as well as a malfunction in the brain's noradrenergic, serotonergic, dopaminergic, and GABA neurotransmitter systems, as agents that modulate their concentration have been shown to have a significant effect on the disorder pathophysiology [6, 8, 11]. Presynaptic norepinephrine auto-receptors are sensitized to norepinephrine activation in panic disorder, according to noradrenergic hypotheses. According to studies, the absence of central control and low levels of Gamma-aminobutyric acid (GABA) in PD leads to greater anxiety during panic attacks. Additional brain imaging investigations have discovered various alterations in specific locations, such as enhanced flow and receptor activation in the limbic and frontal lobes. The amygdala is thought to be the primary source of malfunction [9, 12]. Victims inherit a sensitive "central nervous system fear pathway, focused in the amygdala," according to Gorman et al., but multiple additional brain circuits are also involved [10]. Panic attacks in panic disorder, according to one psychological paradigm, appear due to "fear of fear." According to this paradigm (Figure 1), physical symptoms produced as a result of worry, such as

pounding heart, trembling, shortness of breath, or chest discomfort, are regarded as signaling sensations to start another anxiety cycle. "I'm going to faint, will have a heart attack, and I will now die," is the victim's lone thought at that moment that fails to break down the anxiety cycle. This results in hyper-alertness about bodily sensations, sympathetic nervous system activation, hyper-somatic sensations, and uncontrollable anxiety, all of which finally trigger the panic attack [13, 14].

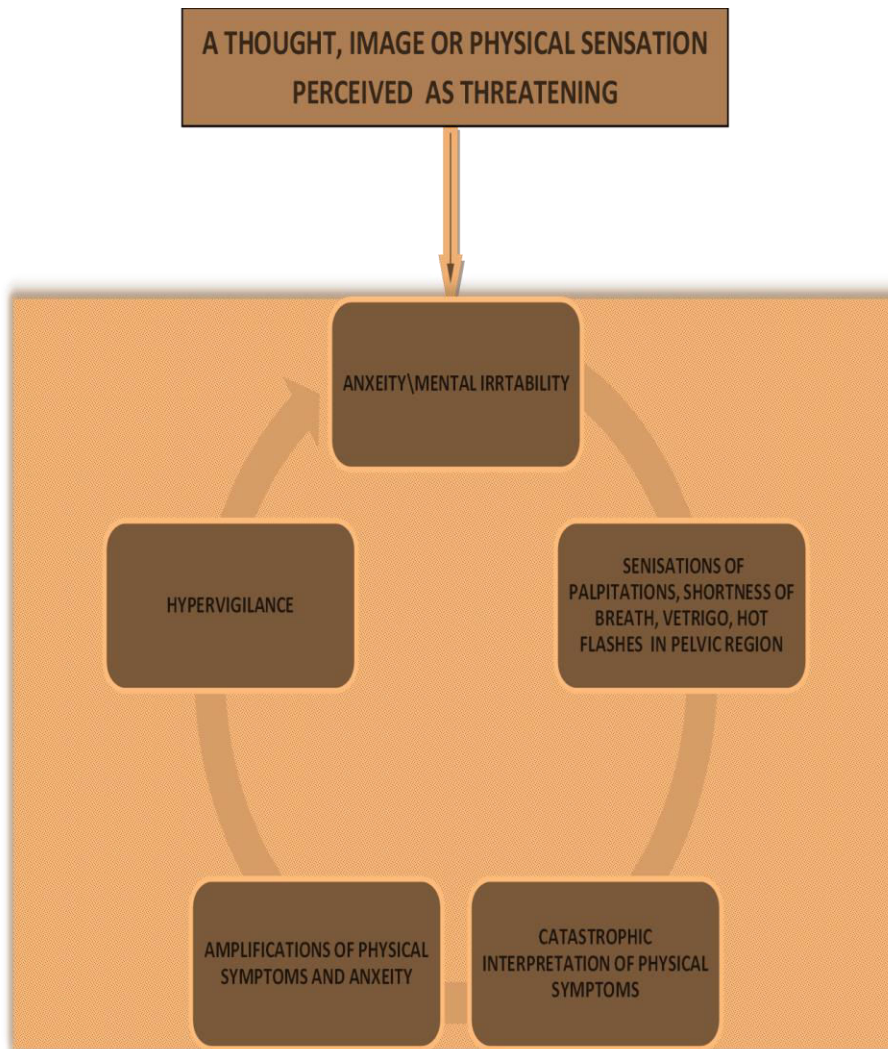


FIGURE 1: Cognitive "fear of fear" model of panic disorder

MANAGEMENT VIA PHARMACOLOGICAL INTERVENTION

There are multiple strategies for resolving this condition, regardless of the various factors that contribute to it. Anxiety disorders and panic disorder are mainly treated with psychotherapy and medications. Combining them is likely to be the most successful technique. Unless a comprehensive and long-term treatment strategy for panic disorder is in place, therapy for panic disorder should not be limited to providing first aid during panic episodes (typically by administering diazepam intramuscularly in an emergency) [15, 16]. Antidepressants like selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), and tricyclic

antidepressants (TCAs), have enough evidence to justify their use in panic disorder treatment. SSRI/SNRI drugs have been found to be useful in the treatment of panic disorder in clinical studies and are now recommended therapy. These drugs have a reduced risk of addiction and abuse than benzodiazepines [3, 8, 16, 17]. The dose, consistency of use, duration of use, consideration of their peculiar mental effects during the early period of use, and finally gradual withdrawal of these antidepressants are all key considerations in their administration. The delayed onset of action of these antidepressants distinguishes them from the agents that produce rapid action. SSRIs increase serotonin levels in the brain by blocking serotonin reabsorption (reuptake) into neurons. The proposed mechanism of action of SNRIs is to inhibit serotonin and norepinephrine reuptake. In contrast to benzodiazepines, which increase GABA within one hour of treatment [18, 19], these drugs require 4-5 weeks to show favorable effects. Patients are sometimes perplexed about the usage of SSRI/SNRI medicines since they do not respond even after three weeks of treatment. As a result, patients cease using them before they can carry out their plan of action, opting instead for fast-acting benzodiazepines, on which they progressively grow reliant and eventually addicted. Benzodiazepines reduce panic episodes temporarily until they are concentrated in the blood, but they do not alleviate panic disorder permanently. After patients take them for longer durations, benzodiazepines become the triggers of panic attack after their half-life in the blood. As a result, longer-term usage of benzodiazepines may exacerbate the panic disorder. Because of the potential for addiction and abstinence syndrome, benzodiazepines should be used only for a few weeks with long-acting antidepressants like SSRIs or only in SOS situations. Patients should take SSRI/SNRI antidepressants for 3-6 months at the prescribed dosage as indicated by their doctor/psychiatrist [20]. After 5-7 weeks of adequate usage, the incidence of panic attacks is reduced by around 70% to 80%. Most patients experience severe anorexia, sexual dysfunction, frequent yawning, mood disorders, palpitations with hot flashes, lower BP, severe chaos, and confusion in the first 10-20 days of treatment. These antidepressants may, in some situations, worsen the severity of panic attacks during the first few weeks of treatment. These are some of the additional reasons why people cease using SSRI/SNRI antidepressants soon after starting them and instead opt for anxiolytics such as benzodiazepines [21]. The optimum pharmacological combination for panic disorder is to start with a benzodiazepine/beta-blocker and SSRI/SNRI for just 10-15 days, then progressively reduce the dose of benzodiazepine. Finally, benzodiazepine should be withdrawn gradually and only SSRI/SNRI should be taken for a minimum of six months to one year depending on the severity of the disorder. This strategy may subside the said effects of SSRI/SNRI that they are posing initially. The majority of guidelines cite expert advice and suggest taking medication for at least a year. When the course of therapy is completed, these drugs should be progressively withdrawn using a dose-decreasing technique. It can induce significant withdrawal symptoms and, in rare cases, revert panic disorder to its previous state if suddenly stopped. Thus, gradual withdrawal of these antidepressants is cardinal upon their caseation. Using these agents for more than a year and in high doses may lead to a fatal condition termed serotonin syndrome or serotonin toxicity [22].

A strategy of proper initiation, duration, and caseation of SSRIs, SNRIs, and TCAs has been revealed to significantly reduce the severity of panic attacks. The patients who recovered with this therapy are said to be susceptible to panic disorder as the disorder may anytime revert in his/her life following periods of extreme anxiety/depression or events of trauma, especially in patients with agoraphobia [23]. If this is the case, the patient should go for the same type of SSRI/SNRI that was administered previously. By doing so, the patient may respond quickly without initial exaggeration

of panic attacks by the use of SSRI/SNRI agents. It is because the previously used antidepressant say fluoxetine will quickly suit the body chemistry as it had already undergone interactions in the neurotransmitter systems. As a result, it is critical to consider these aspects in the individual selection of antidepressant agents. To avoid or at least lessen undesirable effects, it is also recommended that the starting daily dose of these antidepressant drugs is lower than the specified effective dose and that the daily dose be progressively increased over the first weeks of therapy [24]. Patients with panic disorder should be educated about the delayed start of the effect of SSRI/SNRI medications. Only after several weeks of therapy should the outcome be judged. As first-line therapy for panic disorder, both SSRIs and SNRIs are mostly recommended. Antidepressants that operate on the serotonergic system, such as fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, the SNRIs duloxetine, and venlafaxine, and the TCAs clomipramine and imipramine are useful in the long-term treatment of the panic disorder. The most recommended and successful SSRIs for the treatment of panic disorder are fluoxetine and paroxetine. These agents do not initially exaggerate panic attacks as much as other members of the group do. The majority of persons with panic disorder do not tolerate sertraline well. It has been discovered that in most PD patients, this agent amplifies panic episodes while also causing a lot of chaos and confusion in the beginning, and it is also linked to a lot of adverse effects [25].

THE INTERVENTION OF COGNITIVE BEHAVIOR THERAPY

CBT (cognitive behavioral therapy) is a form of psychotherapy that teaches patients with panic disorder (PD) how to notice and change harmful or disturbing thought patterns that appear right before a panic attack [17, 26]. From formal psychotherapies to self-help tools, cognitive behavior therapy encompasses a variety of cognitive techniques and behavioral tactics to treat ideas, attitudes, and behaviors. Cognitive behavioral therapy focuses on modifying reflexive negative ideas that develop and aggravate emotional problems, such as overwhelming anxiety during panic attacks. Cognitive behavioral therapy is utilized in a wide range of therapeutic interventions. While each approach of cognitive behavioral therapy has its own technique, they all aim to change the underlying thinking patterns that cause emotional trauma. Cognitive therapy aims to identify and correct erroneous or distorted mental processes, emotional reactions, and behavior patterns. In the behavior portion, victims are urged to address or confront their dreaded feelings in seemingly safe conditions. Dialectical behavior therapy focuses on ideas and actions while also including tactics like coping skills and attentiveness. Analyzing illogical thoughts, aggressively questioning these beliefs, and eventually resolving to recognize and modify these thinking patterns are all part of rational emotive behavior therapy (REBT) [27]. The cornerstone of Cognitive Behavioral Therapy [CBT] is based on animal evidence of fear habituation. The utilization of realistic events or triggers, as well as responses to internal indications such as increased heart rate, laborious breathing, and bewilderment, has recently been broadened [28]. For instance, a sufferer who is afraid of a heart palpitation may be instructed to jog on the spot in the psychiatrist/counselor's office while the doctor observes and analyses fears such as "My heartbeat is so rapid, I'm going to die". Most psychotherapies for panic disorder include breathing reconditioning, in which victims are instructed to breathe deeper, and more consistently, and has been shown to have a relaxing effect. NICE guideline 22 prescribes 7 to 15 hrs. of CBT over the course of 4 months, conducted in one to two hour weekly sessions [29]. Despite the fact that muscle relaxation methods are advantageous and can be learned through CDs, structured research has indicated that muscle relaxation is less successful in the treatment of panic disorder than cognitive treatments. According to a recent

massive, worldwide controlled experiment, brief cognitive behavior therapy of 6 to 8 hrs. of treatment, supplemented by hand-held computers or guides reduced panic attacks in the majority of patients and was equally efficient as longer therapies.

SELF-HELP THERAPY AND ITS STRATEGIES

In the current day, most people share a common misconception that opting for clinical medicines and drugs is the most efficient way to treat a disorder. This misconception, leads many to directly go for medicinal approaches whenever they find themselves in any sort of distress, be it physical or mental. Although western medicine has made great success in the last few decades, and is very effective in treating several ailments, when it comes to psychological disorders, like panic and stress disorders for example, another viable method to try out is known as ‘Self-help’. Lately, a great number of psychologists and psychiatrists have started understanding and suggesting the significance and effectiveness of self-help strategies to patients who could benefit from it [30]. As the name itself suggests, self-help refers to methods and practices that one could carry out by oneself to alleviate mental stress and agony. Parallely, self-help groups on the other hand, are gatherings of people suffering from such mental distress and emotional traumas where they can freely talk about what they are dealing with. While some people may or may not feel very comfortable with sharing personal information and experiences about themselves, self-help groups target at overcoming individual mental distress by the act of sharing individuals’ personal experiences. A simple way of looking at this approach in layman terms would be ‘sharing is caring’. One of the prime aspects that self-help therapy strategies focus at is our food habits. More and more research is being conducted about how our mental health is related to the food we eat. Although the biochemistry behind it is still newly found and quite complicated, there are a few basic principles behind it that can easily be understood by people lacking great insights in the field of biochemistry. Furthermore, these principles can quite easily be implemented by patients suffering from mental disorders in their daily food habits. One of the main constituents of our food is sugar. Interestingly, sweetness is the only taste which is recognised by the human tongue at the time of infancy. Thus, it can be understood why even in adolescence and adulthood, most people are more affine to foods which are sweet to taste. But processed sugars like the kinds used in commercial food items and beverages are known to have quite a few adverse effects in a person’s health. Refined sugars have been known to increase the risk of several physical and mental ailments [31]. It has been observed that such sugars have subjected several individuals to problems such as depression, anxiety and in some cases even dementia. A simple way of avoiding such cases is to switch refined sugars to natural sugars. Instead of having a can of cola per-se, one could have a glass of natural fruit juice, which would not only have a similar taste factor but also important nutrients such as vitamins, minerals and dietary fibres which would all contribute positively to one’s gut health which in turn have positive upshot on the mental health.

Another substance that the common man finds in his daily food habits is caffeine. Caffeine by itself is known to cause dependency amongst consumers. Although it is commonly wrongly known to be addictive, caffeine is not actually an addictive substance since it causes small amounts of rise in the blood dopamine levels which is not sufficient enough to cause massive imbalances in our nervous system [32]. Initially, caffeine was used for increasing ‘alertness’ in people and prevent drowsiness, over the years, a major part of the general masses started consuming caffeine at significant levels which has brought in observable changes in its targeted functionality. Chemically, caffeine is a

stimulating compound which means that it increases brain activity. It also causes a small surge in the levels of chemicals in the blood such as cortisol and adrenaline. In small amounts, it can hence make a person feel refreshed, but just as easily can cause related adverse effects if consumed in large doses [33]. A common side-effect in individuals with over-usage of caffeine is restlessness. It can be simply understood what prolonged restlessness can do to a patient already suffering from mental disorders like stress and anxiety. Large, continued doses of caffeine are also known to directly cause insomnia and anxiety in people in several recorded cases. Hence, limiting the amount of daily caffeine intake, if not completely stopping it can have significant changes in a person's mental health. When it comes to food habits, hydration definitely is one of its key focuses. Water acts as a medium for all metabolic activities in the body. It acts as a temperature regulator in the body and helps in maintaining homeostasis. The human body consists of almost seventy five percent of water. Dehydration commonly results in a state of imbalance in dopamine and serotonin levels of the brain, which majorly control depression and anxiety levels of a person [34]. Even the smallest amount of dehydration causes a disruption in the homeostatic function of the brain. Such conditions can adversely affect the cognitive functioning of the brain. So, it goes without saying that staying properly hydrated can hugely impact an individual's physical and mental well-being. It has been conventionally recorded that sleep and mental health go hand in hand. Studies have shown that the levels of the hormone cortisol, also known as the stress hormone, decreases during the first few hours of sleep [35]. As stress is directly a function of cortisol levels in the blood, this suggests that while sleeping, an individual is relieved of stress. Sleep also plays an important role in controlling the metabolism of the body as well as release of other significant hormones. Sleep also helps restore 'freshness' of the mind and body as it provides the muscles a chance to relax and replenish themselves with required oxygen and nutrients from the blood. Just like sleep impacts mental health in a positive way, certain mental ailments also cause the loss of proper sleep. Insomnia and anxiety being noteworthy in the case [36]. Conclusively, there are multiple approaches to tackle mental disorders. Although drug intervention has proven helpful in the matter, trying out alternative therapies which do not directly include pharmacological means has also grown popular in recent times. It's likely that combining these approaches will be more effective in the management of PD than using just one.

CONCLUSION

Panic disorder is said to have no exactly known aetiology. This disorder is marked by recurrent, unexpected panic attacks. Its emergence is believed to be influenced by a number of factors, and there is presently no biological test for it. The neurotransmitter systems of norepinephrine, serotonin, dopamine, and gamma-aminobutyric acid (GABA) have been hypothesized to play a vital role in all instances of panic disorder. Panic attacks and panic disorder, according to one psychological paradigm, represent "fear of fear." Most panic disorder sufferers avoid situations where they expect that they could have a panic attack, and this avoidance can severely limit their lives. In the bulk of serious proof-based research on panic disorder and agoraphobia, the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) criteria are employed. Because of the nature of antidepressant interactions with body chemistry, it's vital to look at the proper dosage, length and consistency of usage, and eventual withdrawal. It is well known that combining strategies such as psychoeducation, psychotherapy (especially CBT), lifestyle changes, and medication is more beneficial than utilizing only one. According to NICE guideline 22, psychotherapy, medications, and self-help (bibliotherapy) are all beneficial and should be offered to

patients, taking into consideration their preferences and previous treatment(s).

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