Review

Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 2022; 14(1):46-56

DOI: 10.18863/pgy.940071

Adult Separation Anxiety Disorder: A Review

Yetişkin Ayrılma Anksiyetesi Bozukluğu: Bir Gözden Geçirme

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ABSTRACT

Separation anxiety is excessive anxiety in separation from or expectation of separation from basic attachment figures. Separation anxiety disorder was considered a childhood and adolescent disorder until the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Nowadays, it is known that separation anxiety disorder may continue or begin in adulthood. Adult separation anxiety disorder (ASAD) shows similar clinical manifestations than in the children population. ASAD has been associated with several comorbid mental disorders such as anxiety disorders, post-traumatic stress disorder, and personality disorders. ASAD can also affect the clinical symptoms and course of comorbid psychiatric disorders. There is not enough data about the treatment approaches for ASAD.

Key words: separation anxiety, review, adulthood

ÖZ

Ayrılma anksiyetesi; bireyin temel bağlanma figürlerinden ayrılma ya da ayrılma beklentisi durumlarında aşırı kaygı yaşamasıdır. Ayrılma anksiyetesi bozukluğu, Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabının beşinci (DSM-5) baskısına kadar çocukluk ve ergenlik dönemi bozukluğu olarak kabul edilmekteydi. Günümüzde ayrılma anksiyetesi bozukluğunun yetişkinlikte devam edebildiği ya da başladığı bilinmektedir. Yetişkin ayrılma anksiyete bozukluğu (YAAB) çocukluk dönemindekine benzer klinik belirtiler göstermektedir. YAAB'nin, anksiyete bozuklukları, travma sonrası stres bozukluğu, kişilik bozuklukları gibi çeşitli komorbid ruhsal hastalıklarla ilişkili olduğu gösterilmiştir. YAAB eşlik ettiği diğer psikiyatrik bozuklukların klinik belirtilerini ve gidişatını etkileyebilmektedir. YAAB'ye yönelik tedavi yaklaşımlarıyla ilgili yeterli veri bulunmamaktadır.

Anahtar sözcükler: ayrılma anksiyetesi, gözden geçirme, yetişkinlik

Introduction

Separation anxiety was first defined as a disorder on the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) (American Psychiatric Association 1987). In the past years, separation anxiety disorder (SAD) was usually considered a mental disorder seen during childhood, which did not continue into adulthood. Outdated classification systems included an age criterion, requiring that the disorder develops before the age of 18 (APA 1987, 2004). Due to this age restriction on the diagnosis of SAD, studies often addressed the question of whether the symptoms of SAD extend into adulthood and whether they develop during adulthood. In their study, Costello et al. (2003) reported that the onset of separation anxiety in childhood age is limited only to childhood and that it does not continue into adulthood. In their 3-year observational study, Foley et al. (2004) stated that, in a number of children with SAD, the symptoms would disappear over time, and argued that the disorder was limited to childhood and adolescence. However, the studies conducted in the last 30 years have shown that the main symptoms of separation anxiety can also persist in adulthood (Manicavasaga et al. 1997, Silove et al. 2002) and that adult SAD is more common than previously anticipated (Mayseless and Scher 2000, Cyranowski et al. 2002). There are also studies substantiating that SAD symptoms can first occur in adulthood as well (Shear et al. 2006).

With the studies having demonstrated that SAD can continue into or develop in adulthood, DSM-5 was published in 2013, classifying separation anxiety, which had been considered a childhood disorder until then, as a disorder affecting all age groups that can be diagnosed throughout individuals' lifetime (APA 2013).

The present review investigated the studies conducted to date and attempted to explicate the definition, etiology, epidemiology, clinical characteristics and prognosis of SAD.

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Definition

Anxiety is a state of nervousness and unease of largely unknown origin (Karamustafalıoğlu and Yumrukçal 2011). And separation anxiety is a state of extreme distress caused by separation from the main attachment figure due to death, divorce, illness and other causes. This form of anxiety is not only experienced in actual separation situations but can be seen when there is an expectation of separation as well. Separation anxiety is essentially based on the attachment theory (Bowlby 1973, Ainsworth 1982, Taşdemir et al. 2016).

Separation anxiety is observed particularly in babies up to 1 year of age after separation from their mother or caregiver, caused by a sense of threat to their self-being. This anxiety is relieved by the caregiver. It usually emerges in the eighth month, reaches its climax in the 12th-15th months and subsides in 3 to 5 years of age (Bowlby 1973, Bowlby 1980). Separation anxiety, however, is not considered a deviation from the norm in children, as it indicates healthy cognitive development. This is a developmental-adaptive mechanism that helps the child, who is incapable of self-protection, to keep his mother or caregiver around (Bowlby 1973). Sometimes, a short-term, albeit limited, separation anxiety can be seen in children who start school. SAD is diagnosed when it persists for an extended period of time, is severe, and developmentally inappropriate or impairs functionality (Bögels et al. 2013).

It is stated that the symptoms of separation anxiety in adulthood can turn into excessive anxiety not only with regard to separation from parents, but "separation from spouse or children" or "the notion that harm will come to them". It has been suggested that leaving home, having children, and having an emotional relationship may arouse separation anxiety (Bögels et al. 2013). Individuals diagnosed with adult separation anxiety disorder (ASAD) worry excessively in cases of separation from major attachment objects (spouse, child, mother, father, etc.), feel the need to be constantly close to them, and in time, become inseparable from the attachment objects (Mayseless and Scher 2000). Adults with SAD frequently report having symptoms of separation anxiety early on in their lives, and this data suggests a continuity between the child and adult forms of SAD (Manicavasaga et al. 1997).

Epidemiology

In the National Comorbidity Survey Replication (NCS-R) evaluating adults, the lifetime prevalence of ASAD was reported as 6.6%, while its one-year prevalence was 1.9% (Shear et al. 2006). ASAD symptoms has been established to often begin in adulthood; only one third develop in childhood and extend into adulthood (Shear et al. 2006). The study conducted by evaluating the data obtained from the World Mental Health Surveys of the World Health Organization (WHO) found that the prevalence of SAD has a high rate of 4.8% in the community-based population of approximately 39 thousand from 18 countries, while 43.1% of the sample group had developed the disorder after the 18 years of age (Silove et al. 2015).

Manicavasagar et al. (2000) investigated SAD in adult patients with panic disorder and generalized anxiety disorder, and SAD comorbidity was diagnosed in nearly half of the sample group. A recent study conducted in Turkey, where patients diagnosed with generalized anxiety disorder were evaluated, established co-diagnosis of ASAD in 45% of the patients (Demir and Görgülü 2020).

There are studies investigating the prevalence of SAD that include different age groups. A study evaluating university students found the incidence of ASAD to be 21%, while two other studies found it to be 6% in a geriatric group including participants over the sixty years of age, and 24.5% in pregnant women who were admitted to the hospital's antenatal clinic (Wijeratne and Manicavasagar 2003, Seligman and Wuyek 2007, Eapen et al. 2012).

The studies also evaluated whether the diagnosis of ASAD was childhood or adult-onset. In the national comorbidity survey, it was found that 77.5% of the patients with ASAD at any point during their life and 75.2% of the patients with ASAD in the 12-month period were diagnosed with adult-onset SAD (Shear et al. 2006). A clinical study demonstrated that adult-onset separation anxiety and separation anxiety that persists from childhood into adulthood have similar rates (Pini et al. 2010). There are, however, various other study results showing that the ratio of adult-onset separation anxiety to all separation anxiety is 1/4 to 1/3 (Manicavasaga et al. 1997, Silove et al. 2010). In a study on anxiety that develops after starting school, it was found that 16 out of 72 individuals were diagnosed with ASAD and 25% of those were adult-onset (Silove et al. 2002).

During childhood, SAD (CSAD) is usually detected between 7 and 8 years of age (Alfano et al. 2002, Bögels et al. 2003). It is emphasized that CSAD develops in early childhood, that separation anxiety developed in childhood and extending into adulthood occurs in their teens, and adult-onset separation anxiety begins in the 20s (Shear et al. 2006). Separation anxiety is exceedingly rare in individuals over the age of sixty, and reasons such as settling in a nursing home or the death of loved ones in later ages can lead to separation anxiety (Wijeratne and Manicavasagar 2003).

In a study investigating a sample group diagnosed with anxiety disorders and/or depressive disorder who were admitted to the psychiatry outpatient clinic, 24% of the males and 30% of the females were diagnosed with ASAD (Cyranowski et al. 2002). In community screenings, the diagnosis of ASAD was seen to be 1.4 times higher in females. However, it has been stated that the diagnosis of CSAD is especially high in females, while the gender difference becomes smaller in ASAD (Shear et al. 2006). The results of the study also suggest that adult-onset ASAD is more prevalent among males (Shear et al. 2006, Silove et al. 2010). To summarize the results of the study; SAD is more prevalent in females during both adulthood and childhood, while the prevalence of adult-onset SAD is higher than childhood-onset

SAD in males. Such high rates can be accounted for by the fact that the rate that separation anxiety persists from childhood into adulthood is higher in males than in females, or that it is more likely to develop in adulthood in males than in females.

It was found that the patients with ASAD in the community samples had lower level of education, and the rate of unemployment and being single-divorced were higher than the healthy controls. It is reported that as age and the duration of education increase, the rate of ASAD decreases (Shear et al. 2006). However, in a clinical study contradicting these data, it was found that ASAD is not associated with marital status, unemployment and level of education (Pini et al. 2010).

In addition to sociodemographic data, separation anxiety is also expected to be affected by cultural structures. Most of the studies on maternal separation anxiety are conducted in Western societies, that is, in individualistic cultures. Since separation anxiety is associated with a more limited differentiation of self and interconnectedness is more important in collectivist cultures than in individualistic cultures that focus more on independence, it is suggested that separation anxiety symptom levels may be higher in collectivist cultures. However, considering that anxiety should be excessive according to cultural norms, SAD can be higher in individualistic cultures as well (Heinrichs et al. 2006). Furthermore, actual threats that increase the likelihood of losing a loved one -such as war, poverty, or living in a dangerous environment- can affect separation anxiety, and SAD may therefore be more common in cultures more exposed to such conditions (Peleg et al. 2006).

Etiology

The development of separation anxiety originates from the attachment theory. According to the theory, the manner of coping with the stress adopted after separating from the attachment figure plays the key role in the child's regulation of their emotions and sense of trust. It is known that the very first relationship established with the caregiver(s) guides the close relationships to be established later on. This is why the type of attachment between the caregiver and the infant is crucial (Weinfield et al. 1997, Ditommaso et al. 2003). Negative parenting styles (critical, overprotective, negligent, etc.) may result in the child's needs being met in an unhealthy way during the early period. Problematic or poor attachment styles are considered as a risk factor for many psychological problems not only in childhood but in adulthood as well (Weinfield et al. 1997, Başbuğ et al. 2016).

Maternal separation anxiety is thought to play an effective role in the development of CSAD. In maternal separation anxiety, the mother having a less mature personality, low self-esteem, negative self-perception, inadequate coping methods in the face of rejection, insecure attachment figures, and courage after leaving her own family were found to be significant. It has been stated that high level of anxiety developed in the mother after separation causes her to be insecurely attached to her baby, to develop insecure behaviors about baby care and to be overprotective. These results are believed to also play a role in the development of separation anxiety in children (Hock et al. 1989).

It has been reported that mothers of individuals with ASAD are generally overprotective, which may lead to anxious attachment style (Manicavasagar et al. 1999). Manicavasagar et al. (2009) found that there is a stronger correlation between ASAD and the "anxious attachment style" compared to patients with panic disorder, and that patients with ASAD have a higher need for validation.

Although studies on the etiology of separation anxiety have not produced clear results, there is evidence pointing to its association with neuroticism. It has been suggested that anxiety and mood changes have a genetic background in neurotic individuals with separation anxiety (Lahey 2009), and it has been argued that this genetic background is more prominent in females (Eaves et al. 1997). A previous study demonstrated significant elevations in the neuroticism-related scores of the cases diagnosed with ASAD (Silove et al. 2010). Some researchers also argued that the relationship between neuroticism and separation anxiety is non-specific and that it is a part of the interpersonal relationship (Wilhelm et al. 2004).

Genetics and Neurobiology

Genetic studies on adult separation anxiety are limited, mosty focusing on CSAD (Roberson-Nay et al. 2012). It has been demonstrated that school refusal is more common in siblings or children of individuals who suffered from separation anxiety during childhood (Silove et al. 1993). A high incidence of SAD is found in the 1st and 2nd degree relatives of children with SAD. There is evidence in family studies that SAD is inherited within the family. Maternal separation anxiety has been proven to be significantly related to the separation anxiety in the child (Peleg et al. 2006). It has been reported that not only the diagnosis of ASAD, but also other parental anxiety disorders pose a risk for CSAD (Nestadt et al. 2001, Strober et al. 2007).

In a study in which children diagnosed with CSAD and their families were evaluated in order to examine the family-child harmony in terms of SAD, at least one family member in 63% of the children was diagnosed with ASAD. These families also reported high levels of separation anxiety for their own childhood (Manicavasagar et al. 2001).

In the twin study, it has been suggested that familial clustering characteristics are stronger for mothers and daughters, and female gender may prove a stronger genetic burden for separation anxiety (Silove et al. 1995). In studies conducted in monozygotic and dizygotic children, lifetime prevalence of separation anxiety was found to be high, while it was higher in monozygotes (Bolton et al. 2006, Ehringer et al. 2006, Ogliari et al. 2010). Despite these results, it was emphasized that the environmental impact is important in the development of SAD (Eley et al. 2008). It has been stated that this whole genetic effect is not just seen in separation anxiety, but also in other anxiety disorders, and that genetics only play a minor role in the disorder (Gregory and Eley 2007).

There is no well-defined biomarker for separation anxiety. It has been shown that the density of 18 kDA translocator protein

(TSPO) (formerly defined as peripheral-type benzodiazepine receptor binding domains) in platelets changes in the presence of acute or chronic stress in anxiety disorders (Da Pozzo et al. 2012). In the conducted studies, it was found that, among the patients diagnosed with bipolar disorder (Abelli et al. 2010) and panic disorder (Pini et al. 2005), only those accompanied with ASAD had significantly lower TSPO levels, and that, in patients diagnosed with depressive disorder (Chelli et al. 2008), a decrease in the TSPO intensity associated with ASAD symptoms was detected. Also, the substitution of Ala and Thr in the 147th region of the translocator protein was found to be associated with adult separation anxiety in patients with depression (Costa et al. 2009a). In the studies, it has been stated that TSPO level is a non-specific biomarker, especially due to accompanying psychopathologies (Pini et al. 2005, Chelli et al. 2008).

It is known that oxytocin is a neurotransmitter/neuromodulator that affects attachment processes and plays a role in the development of social bonds (Tops et al. 2007). The hypothalamo-pituitary-adrenal system is linked to the oxytocinergic system. It was found that attachment anxiety in adults is associated with the cortisol response to acute stress (Quirin et al. 2008), and that positive attachment reduces stress by regulating oxytocin and cortisol levels (Tops et al. 2007). A study involving administration of oxytocin to adults who had suffered early parental loss found a weakened cortisol reduction response to oxytocin (Meinlschmidt and Heim 2007). Thus, oxytocin and separation anxiety are thought to have a potential relationship (Costa et al. 2009b). There are a limited number of studies on the subject in patients diagnosed with ASAD. In a genetic study, mutations and polymorphisms in the oxytocin prohormone region and promoter region were examined (Costa et al. 2009b). In a study examining three groups -depressive disorder, ASAD accompanying depressive disorder, and control group-, polymorphism rates were found to be close. Based on the study data, it was reported that oxytocin plays a role in separation anxiety along with numerous other mental disorders (Costa et al. 2009b).

Besides oxytocin, molecular genetic studies on attachment have also focused on dopamine and serotonin receptor genes. It was shown that the DRD47-repeat polymorphism in the dopamine gene plays a role in the mother's attachment issues due to loss or trauma. There are studies further supporting that this gene might play a role in CSAD (Van Ijzendoorn and Bakermans-Kranenburg 2006, Gadow et al. 2010). Another study found that polymorphism in the DRD2 dopamine receptor gene was associated with anxious attachment, and the polymorphism in the 5HT2a serotonin receptor gene was associated with avoidant attachment (Gillath et al. 2008).

There is a known relationship between panic disorder and carbon dioxide (CO_2) hypersensitivity. In a study conducted in patients diagnosed with ASAD, it was found that patients with panic disorder had similar rates of CO_2 hypersensitivity (Atlı 2011). The results of the study suggested that CO_2 hypersensitivity may be a common biomarker in panic disorder and SAD (Pine et al. 2005).

It has been demonstrated that all anxiety disorders, not only limited separation anxiety, but especially including generalized anxiety disorder (GAD), social phobia (SP) and Williams Syndrome, are associated (Leyfer et al. 2009).

Neuroimaging

There are a limited number of neuroimaging studies and attachment anxiety has been associated with a reduction in left hippocampal volume (Quirin et al. 2010). An increase in left amygdala activity was detected when angry faces were shown to adults with anxious attachment associated with SAD (Vrtička et al. 2008). Administration of oxytocin has been shown to regulate amygdala responses to frightening visual images (Kirsch et al. 2005).

There are existing study results on the relationship between SAD and memory deficit. In a study involving visual and auditory memory functions conducted on children and their families, it was emphasized that auditory memory deficit was not associated with CSAD, while visual memory deficit may be associated (Vasa et al. 2007). In another study, it was argued that auditory and visual memory deficits are predictors for all anxiety disorders, including SAD (Pine et al. 1999).

Environmental Risk Factors

Early life events and childhood traumas are known to play an active role in the development of psychopathology. SAD symptoms may occur after a particularly negative life event such as the loss of a parent (Alkın 2010).

Behavioral-genetic studies on CSAD show that environmental risk factors are important, especially in male children, but similar studies were not conducted for ASAD. Studies on comorbidity offer insight on possible environmental risk factors for ASAD. Frequent co-existence of ASAD and post-traumatic stress disorder suggests that fear of trauma is a risk factor for ASAD, and the strong relationship between ASAD and prolonged grief suggests that loss of a loved one is another risk factor (Bögels et al. 2013).

Parenthood is thought to be another possible environmental risk factor for ASAD. Parental intervention in children was demonstrated to be associated with SAD (Wood 2007). The retrospective reports of maternal overprotection were also found to be correlated with ASAD in adults (Manicavasagar et al. 1999, Bögels et al. 2013).

Environmental risk factors for ASAD can be associated with certain developmental periods. Therefore, children becoming independent may become an environmental risk factor for ASAD depending on the quality of the attachment relationship (Bögels et al. 2013).

Clinical Features and Diagnosis

Separation anxiety symptoms in adulthood turn into extreme anxiety and fear of being separated from a spouse or children or of potential harm coming to someone close to them, on a

similar level to that of separation from parents (Manicavasaga et al. 1997). Patients with ASAD are in a state of deep anxiety due to their need to maintain intimacy or close contact with their attachment figures (Silove et al. 2007), and such individuals describe their anxiety as 'excessive, egodistonic and restrictive' (Manicavasagar et al. 2010). They have a difficult time controlling their anxiety and keeping it from being reflected on their behavior. Just as children refuse to go to school to be able to stay at home, adults too might be unwilling to go to work (Manicavasagar et al. 2009). They struggle to maintain intimacy through coping or avoidance behaviors such as going to work late or not going at all, spending time at home, and refusing to go to another city to study (Alkın 2010). Nightmares involving the theme of separation are common and they avoid sleeping alone. They may have a panic attack in case of actual or anticipation of separation (Manicavasaga et al. 1997). In a study, more than half of the patients stated that they felt safer at home alongside their loved ones (Seligman and Wuyek 2007).

Separation anxiety symptoms seen in childhood and adulthood are similar except for a few differences (Silove et al. 2010). Physical symptoms such as nausea and abdominal pain are predominant in childhood separation anxiety, while cognitive and emotional symptoms are predominant in adulthood (Silove et al. 2007).

DSM-IV-TR classified SAD among the category of other disorders of infancy, childhood or adolescence under disorders first diagnosed in infancy, childhood or adolescence (APA 1994). In DSM-5, on the other hand, it is classified under anxiety disorders (APA 2013).

Separation Anxiety Disorder DSM-5 Diagnostic Criteria

A. Developmentally inappropriate and excessive fear or anxiety concerning separation from those to whom the individual is attached, as evidenced by at least three of the following:

   1. Recurrent excessive distress when anticipating or experiencing separation from home or from major attachment figures
   2. Persistent and excessive worry about losing major attachment figures or about possible harm to them, such as illness, injury, disasters, or death
   3. Persistent and excessive worry about experiencing an untoward event (e.g., getting lost, being kidnapped, having an accident, becoming ill) that causes separation from a major attachment figure.
   4. Persistent reluctance or refusal to go out, away from home, to school, to work, or elsewhere because of fear of separation
   5. Persistent and excessive fear of or reluctance about being alone or without major attachment figures at home or in other settings
   6. Persistent reluctance or refusal to sleep away from home or to go to sleep without being near a major attachment figure
   7. Repeated nightmares involving the theme of separation
   8. Repeated complaints of physical symptoms (such as headaches, stomachaches, nausea, or vomiting) when separation from major attachment figures occurs or is anticipated

B. The fear, anxiety, or avoidance is persistent, lasting at least 4 weeks in children and adolescents and typically 6 months or more in adults

C. The disturbance causes clinically significant distress or impairment in social, academic (occupational), or other important areas of functioning

D. The disturbance is not better explained by another mental disorder, such as refusing to leave home because of excessive resistance to change in autism spectrum disorder; delusions or hallucinations concerning separation in psychotic disorders; refusal to go outside without a trusted companion in agoraphobia; worries about ill health or other harm befalling significant others in generalized anxiety disorder; or concerns about having an illness in illness anxiety disorder (APA 2013).

The fact that the diagnostic criterion 'the onset is before age 18 years' in DSM-IV-TR is not included in DSM-5 has allowed the diagnosis of adult-onset SAD.

Psychometric Scales Evaluating Separation Anxiety

To assess separation anxiety, Silove et al. (1993) developed the Separation Anxiety Symptom Inventory (SASI). It is a 15-item inventory that retrospectively questions the separation anxiety symptoms that may have been experienced in childhood. Manicavasagar et al. (2003) developed the 27-item Adult Separation Anxiety Checklist (ASAC), a questionnaire about separation anxiety symptoms experienced in adulthood. Turkish validity and reliability of both scales have been proven (Diriöz et al. 2012a).

Cyranowski et al. (2002) developed the clinical interview called Structured Clinical Interview for Separation Anxiety Symptoms. This structured interview developed for use with adults consists of 2 parts containing 8 items each. The former retrospectively evaluates childhood SAD diagnostic criteria, while the latter evaluates adult SAD diagnostic criteria. Its Turkish validity and reliability has been proven (Diriöz et al. 2012b). DSM-5 Separation Anxiety Disorder Severity Scale- adult form is a 10-item self-report scale used to determine the severity of separation anxiety symptoms in adulthood. Since it was prepared in accordance with the DSM-5 diagnostic criteria, it offers help in questioning the symptoms and measuring the severity of SAD. The Turkish version has been proven to be valid and reliable (Coldur et al. 2020).

Parental Separation Anxiety Scale and Maternal Separation Anxiety Scale are used for assessing the separation anxiety parents experience when separated from their children (Hock et

al. 1989, Dashiff and Weaver 2008).

ASAD causes loss of functionality, and disability becomes more severe in the presence of comorbidity (Shear et al. 2006, Kessler and Wang 2008). It has been established that it particularly leads to a loss in occupational and social functions, and that functionality in family relations is relatively preserved even though the relations with the partner are affected (Manicavasaga et al. 1997, Pini et al. 2010). In an epidemiological study, 21.1% of the cases with ASAD reported significant deterioration in housework, 21.7% in business life, 28% in their personal relationships, and 31.5% in their social relationships (Shear et al. 2006). In a study conducted on patients with anxiety and depressive disorders, it was stated that the individuals diagnosed with ASAD suffer significant impact on performance and interpersonal relationships. It was found that the effects of CSAD, childhood-onset ASAD that continues into adulthood, and adult-onset ASAD have a similar effect on the level of functionality (Pini et al. 2010).

Comorbidity

Anxiety disorders, mood disorders, and post-traumatic stress disorder are the most common psychiatric disorders accompanying separation anxiety (Shear et al. 2006). There are study results in the literature for the diagnosis of SAD accompanying mental illnesses, predominantly anxiety disorders.

Comorbidity rates, anxiety disorders in particular, were found to be high in ASAD (Silove et al. 2010). In epidemiological studies, 91.1% of the patients with ASAD were diagnosed with at least one other accompanying psychiatric disorder, and lifetime comorbidity rates were reported as 67% for any given anxiety disorder and as 62% for mood disorder. It was found that those diagnosed with SAD suffered drug abuse 3 times, anxiety disorder 5 times and mood disorders 4 times more often than non-SAD patients (Cartwright et al. 2006, Shear et al. 2006). In their study, Manicavasaga et al. (1997) found the comorbidity of mental disorder at a rate of 67% in patients with ASAD, and reported that 69% of the patients had a lifelong history of major depressive disorder.

A case-control study evaluating psychiatric comorbidities in patients with obsessive compulsive disorder (OCD) found that, in patients diagnosed with SAD, 10.7% had hypochondriasis, 7.4% had panic disorder + agoraphobia, 6.3% had OCD, 4.2% had pathological skin picking and nail biting, 3.7% had generalized anxiety disorder, and 2.6% had major depressive disorder comorbidities (Nestadt et al. 2001). In a recent study, on the other hand, the comorbidity rate of SAD in adults with OCD was found to be 4.4% (Franz et al. 2015).

A study by Silove et al. (2010) involving patients diagnosed with anxiety disorders found that 23% of the samples included panic disorder, 31% panic disorder + agoraphobia, 26% generalized anxiety disorder, and 20% social phobia prior to evaluation of the diagnostic criteria for ASAD. When the distribution of disorders was re-evaluated by taking into consideration the diagnostic criteria for ASAD, it was found that 23% of the patients had ASAD, 12% had panic disorder, 11% had panic disorder + agoraphobia, 21% had generalized anxiety disorder, and 14% had social phobia. The most significant reduction was observed in the panic disorder + agoraphobia group, and 49% of the group was diagnosed with ASAD. Based on this study, it was concluded that panic disorder and agoraphobia may be the most common comorbidities of ASAD (Silove et al. 2010). Manicavasagar et al. (2000, 2009) reported the rates of panic disorder being accompanied by ASAD as 65% and 46% in two different epidemiological studies, supporting the claim that ASAD is often accompanied by panic disorder.

In studies evaluating separation anxiety in Turkey; ASAD was diagnosed at a rate of 54% in patients with bipolar disorder (Tasdemir et al. 2016) and 41% in patients with major depressive disorder (Elbay et al. 2021).

It was reported that non-childhood-onset ASAD may develop after the traumatic loss of loved ones in adulthood, and thus, it is accompanied by complicated grief and post-traumatic stress disorder (PTSD) (Bögels et al. 2013). It was found that patients whose childhood SAD symptoms have persisted into adulthood are at high risk for complicated grief, and SAD plays a mediator role between complicated grief in adults and CSAD. This result suggests that the loss of a loved one may trigger early separation anxiety (Wijeratne and Manicavasagar 2003, Vanderwerken et al. 2006). Complicated grief is associated with ASAD as it can also be triggered by traumatic losses (Wijeratne and Manicavasagar 2003). In a study conducted on patients with ASAD, 33% of the participants reported that they experienced a great loss at the onset of their symptoms (Manicavasaga et al. 1997). A study conducted on refugees found that almost every individual diagnosed with ASAD has an accompanying PTSD diagnosis, but half of those with PTSD have an additional diagnosis of ASAD (Silove et al. 2010). Although most studies reported that ASAD particularly accompanies panic disorder and agoraphobia, it has been suggested that it most frequently exhibits comorbidity with complicated grief and PTSD (Bögels et al. 2013).

In another study evaluating diagnoses of ASAD and dependent personality disorder, which included sample groups with alcohol use disorders, eating disorders and healthy individuals, the current prevalence of ASAD was found to be 2% in the control group, 6% in the alcohol use disorder group, and 15% in patients with bulimia nervosa. The lifetime prevalence of ASAD was reported as 5% in the control group, 16% in the alcohol use disorder group, and 31% in the bulimia nervosa group. According to the results of the study, it was established that the diagnosis of ASAD was most frequently accompanied by bulimia nervosa (Loas et al. 2002).

A study investigating the relationship between ASAD and personality disorders found that the group including patients with personality disorder developed separation anxiety symptoms early, and had higher separation anxiety scores and worse level of functionality (Osone and Takahashi 2006).

Sillove et al. (2010) found that patients with childhood-onset ASAD were more likely to have comorbid personality disorders (clusters B and C) than those with adult-onset ASAD. In a study by Loas et al. (2002) a strong relationship was found between dependent personality disorder and ASAD in the control group. Manicavasaga et al. (1997), however, found that the comorbidity rate of ASAD and dependent personality disorder was only 17%. In another study, similar rates of personality disorder comorbidity were found for ASAD and other anxiety disorders in adult anxiety clinic patients (Manicavasagar et al. 2000). There are mixed results regarding the comorbidity of personality disorders in ASAD, but ASAD does not appear to be specifically associated with dependent personality disorder despite similarities in the diagnostic criteria (Bögels et al. 2013).

Based on the results obtained from previous studies, comorbid anxiety disorders and mood disorders are known to be common in patients diagnosed with CSAD/ASAD. There are studies demonstrating a lack of difference between CSAD and ASAD in terms of comorbidity (Silove et al. 2010). However, potential differences are believed to exist in terms of comorbidity in patients with and without childhood-onset ASAD. Future studies in this area will help clarify the subject further.

Differential Diagnosis

Separation anxiety can be a part of the clinical diagnosis of pervasive developmental disorders, schizophrenia, or other psychotic disorders. If separation anxiety symptoms occur in the presence of these disorders, the diagnosis of SAD is avoided (Mancini et al. 2009, American Psychiatric Association 2013). Unlike hallucinations in psychotic disorders, the unusual perceptual experiences in SAD originate from misperception of a real stimulus and occur only in certain situations, and this perception dissipates around the attachment figure (İlhan 2018).

Some researchers state that separation anxiety precedes other anxiety disorders and panic attacks may be secondary to SAD (Mercer 2006). Patients with SAD may experience "panic", which manifests as extreme stress or distress, but the primary fear here is that of separation rather than that of having a panic attack (Baldwin et al. 2016). While anxiety in SAD focuses on separation from the attachment figure, the focus of anxiety in panic disorder is one's own health and safety (Bögels et al. 2013). Agoraphobic situations, on the other hand, are defined as places or situations where escape may be difficult or where it is impossible to receive assistance. On the contrary, the primary fear in SAD is that something undesirable happens to loved ones or attachment figures (Baldwin et al. 2016).

In children and adolescents with generalized anxiety disorder, the worry that something bad will happen to their parents is among the common findings. This symptom coincides with SAD. However, the worry in generalized anxiety disorder is not limited to that over the parents, and there are major worries that impair the functionality of the person in all areas of life, such as health and financial problems (Bögels et al. 2013).

The diagnosis of ASAD should be differentiated from certain personality disorders. It is crucial to distinguish between ASAD and dependent personality disorder. The main worry in dependent personality disorder is concerning a person's inability to cope with their own physical or emotional state. In ASAD, on the other hand, the main worry is focused on loss. People with dependent personality disorder feel the need to trust others and are random and pervasive, not focused on specific figures (Bögels et al. 2013). Patients with a diagnosis of ASAD experience separation anxiety in relatively more consistent relationships. 'Fears of abandonment or efforts toward not being abandoned' seen in borderline personality disorder can be confused with ASAD. In borderline personality disorder, these fears are usually a result of emotionally intense and unstable relationships. In ASAD, however, separations caused by 'accident, injury, death or other unforeseen event' induce greater fear than abandonment and experienced in consistent and balanced relationships (Cyranowski et al. 2002, Manicavasagar et al. 2010).

Prognosis

In previous studies, ASAD was generally examined as part of other mental disorders and said to have a negative impact on the course of such disorders. It has been emphasized that, in the presence of a diagnosis of ASAD accompanying anxiety disorders, relapses become more frequent, symptoms persist despite treatment, and stronger resistance develops to pharmacotherapy and psychotherapy applications for anxiety disorders (Cartwright et al. 2006, Shear et al. 2006). It was found that, when panic disorder and ASAD is simultaneously present, impairment in functionality is more common and more resistant to medical treatment (Shear et al. 2006, Pini et al. 2014). Studies evaluating the effectiveness of cognitive behavioral therapy (CBT) demonstrated that the response to CBT is reduced when panic disorder is accompanied by ASAD, as is the case with medical treatment (Aaronson et al. 2008, Pini et al. 2012). The study by Silove et al. (2010), which showed that the response to medical treatment and CBT decreased by 3.7 times when panic disorder was accompanied by ASAD, is also consistent with this data. In a study conducted in Turkey evaluating SAD in patients with bipolar disorder, it was found that childhood or adult SAD symptoms negatively affect functionality areas (Sahin et al. 2019). Another study investigating patients with bipolar disorder demonstrated that patients with ASAD have a longer history of suicide attempts and lower levels of functionality (Tasdemir et al. 2016). It has been determined that patients diagnosed with major depressive disorder exhibit more anxiety symptoms and respond sub-optimally to antidepressant treatment when a diagnosis of ASAD accompanies (Elbay et al. 2021).

There are studies on the prognosis of SAD on the adulthood findings of people with a history of CSAD. Studies have shown that some of the cases with ASAD have a history of CSAD, or individuals with CSAD were found to suffer from ASAD in adulthood (Shear et al. 2006). However, it is suggested that CSAD is not only associated with ASAD, but may be associated with all

anxiety disorders. Although CSAD has been suggested as a specific antecedent of panic disorder in previous studies, this claim has not been supported in various subsequent studies (Silove et al. 2002). In the meta-analysis conducted by Kossowsky et al. (2013), it was concluded that the presence of CSAD increases the risk for the development of panic disorder and any anxiety disorder in adulthood, but there is no increased risk for depression and substance use disorders. An annual follow-up study conducted with subjects aged 14-22 years demonstrated that panic disorder and agoraphobia that developed during the 4-year follow-up period were associated with separation anxiety, whereas a similar relationship was not found in other anxiety disorders, alcohol use disorders, and bipolar disorder (Brückl et al. 2007).

While it was expected that SAD with early childhood onset would cause higher rates of ASAD development in adulthood, it was seen that those with mid-late childhood-onset had a higher rate of developing ASAD. In the same group, comorbidity rates of more frequent mood episodes, other anxiety disorders and personality disorders are higher in adulthood. Thus, individuals with severe separation anxiety spanning mid-late childhood and early adolescence are likely to have a worse prognosis overall (Manicavasagar et al. 2010). Episodic course is more common in ASAD that develops secondary to traumatic situations such as divorce and death (Manicavasaga et al. 1997).

Treatment

There is no available standard treatment for SAD. Like other anxiety disorders, it is treated with pharmacotherapy and psychotherapy. Both general CBT and disorder-specific CBT were found to be effective in CSAD. However, it was observed that traditional CBT focusing on other anxiety disorders does not reduce separation anxiety symptoms (Manicavasaga et al. 1997). In CBT applications for CSAD, methods such as parental education, behavior management skills, disorder-specific psychoeducation, correction of dysfunctional cognitions, and exposure and response prevention were found effective (Schneider et al. 2011). It is believed that the Parent-Child Interaction Therapy, which helps improve the behavior of children by altering the child-parent interaction, will prove useful in CSAD treatment (Choate et al. 2005).

There is strictly limited date on ASAD treatment. It has been reported that patients with ASAD comorbidity who undergo CBT for panic disorder are approximately four times more likely to have a negative treatment outcome than those without ASAD comorbidity. These results were thought to be due to lack of cognitive restructuring and the fact that the psychopathology of SAD was not addressed through CBT (Aaronson et al. 2008). CBT specifically focusing on ASAD can reduce separation anxiety and lead to better results (Bögels et al. 2013). It is believed that supportive, emotion-focused therapies that address family and are capable of deducing attachment patterns and emotions of the individual can prove effective (Milrod et al. 2014).

Fluoxetine treatment was found to be effective in patient groups with anxiety disorder, including children with SAD (Bögels et al. 2013). In the pilot study evaluating the patients diagnosed with ASAD who were followed up using vilazodone, a selective serotonin reuptake inhibitor and 5HT1a receptor partial agonist, a more significant improvement was found in separation anxiety symptoms compared to the use of placebo. It was therefore concluded that vilazodone may be effective in the treatment of SAD (Schneier et al. 2017). Separation anxiety is rarely seen in individuals over the sixty years of age. Careful follow-up of these individuals is crucial in preventing the development of other mood disorders (Wijeratne and Manicavasagar 2003).

Conclusion

With the removal of the age criterion in DSM-5, SAD has become a disorder that can be diagnosed at any age. Today, ASAD is known to be a common mental disorder in both genders, and there are attempts to explain its etiology through factors such as attachment theory, genetics, and neurobiology. In the literature, ASAD was frequently examined in association with other mental disorders and has been proven to negatively affect the course and treatment response of a given mental disorder, and may lead to functionality impairment. However, the information on ASAD is still not fully sufficient. There is a need for follow-up studies and investigation of effective treatment approaches in order to determine its effect on the course and the clinical conditions that it may predict. Studies focusing primarily on the diagnosis of ASAD and comparing childhood-onset and non-childhood-onset patients will provide more information about the disorder.

Authors Contributions: *The authors attest that she has made an important scientific contribution to the study and has assisted with the drafting or revising of the manuscript.*
Peer-review: *Externally peer-reviewed.*
Conflict of Interest: *No conflict of interest was declared by the authors.*
Financial Disclosure: *The authors declared that this study has received no financial support.*

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