

## Separation anxiety disorder in the DSM-5 era

C. Carmassi<sup>1</sup>, C. Gesi<sup>1</sup>, E. Massimetti<sup>1</sup>, M.K. Shear<sup>2</sup>, L. Dell'Osso<sup>1</sup>

<sup>1</sup> Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; <sup>2</sup> School of Social Work, Columbia University, New York, USA

### Summary

*Separation Anxiety Disorder has been recently classified into the DSM-5 section of Anxiety Disorders, acknowledging its role not only in childhood and adolescence but also across the whole lifespan. In the DSM-IV-TR, in fact, this condition was typically considered to begin in childhood. Clinical data report prevalence rates from 20 to 40%, showing high comorbidity rates with most mental disorders. Epidemiological data highlight that in fact one third of childhood cases persist into adulthood, while the majority of adult cases reports its first onset in adulthood.*

*In all cases, Separation Anxiety Disorder is associated with a severe impact on the overall functioning. Most relevant research in the field is discussed highlighting the need of a paradigm shift in which clinicians are alerted to identify and treat this condition in all age upon the recent DSM-5 reformulation will be highlighted.*

### Key words

*Separation anxiety • Panic disorder • Anxiety disorders • Complicated grief • Post-traumatic stress disorder*

### Separation anxiety disorder across the DSM-5

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) <sup>1</sup> has recently introduced important classification changes, including the introduction of Separation Anxiety Disorder into the section of Anxiety Disorders. In the DSM-IV-TR <sup>2</sup>, unlike other anxiety disorders, Separation Anxiety Disorder was considered a condition typically beginning in childhood that could be diagnosed in adults only “if onset is before 18 years of age”. For this reason, although most anxiety disorders typically start in childhood or adolescence, this was the only one placed under the label “Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence”. Notwithstanding, the DSM-IV-TR did not actually preclude a diagnosis in adulthood, stating that “adults with the disorder are typically over concerned about their offspring and spouses and experience marked discomfort when separated from them”, such classification led clinicians to usually overlook this condition in their adult patients <sup>3,4</sup>.

By removing the age-of-onset criterion, the DSM-5 acknowledged Separation Anxiety Disorder as a condition that may span the entire life, but also begin at any age, leading to its inclusion among Anxiety Disorders. Despite age of onset before 18 years is no longer needed, the DSM-5 states that it usually begins in childhood and more rarely in adolescence, somehow indicating that first onset in adulthood is uncommon, and that the majority of children with Separation Anxiety Disorder

are considered to be free of impairing anxiety over their lifetime. However, it has been shown that more than one third of subjects classified as childhood cases might persist into adulthood <sup>5</sup> and some epidemiological and clinical data have highlighted that the prevalence of Separation Anxiety Disorder might be greater among adults than in children and that the vast majority of persons classified as having adult Separation Anxiety Disorder report first onset in adulthood, with a peak of onset in early 20s <sup>5,6</sup>.

The essential feature of Separation Anxiety Disorder is an inappropriate and excessive anxiety concerning separation, actual or imagined, from home or major attachment figures, causing clinically significant distress or impairment in functioning. Symptoms may include recurrent excessive stress when anticipating or experiencing separation from major attachment figures or home, persistent and excessive worry about losing major attachment figures or about potential harm befalling to them. Furthermore, in response to fear of separation from an attachment figure, patients may show excessive worry about experiencing a negative event (e.g., an accident or illness, being lost or kidnapped), refusal to leave home to go to school or to work, fear of being alone or without major attachment figures at home or in other settings; reluctance or refusal to sleep away from home or to go to sleep; repeated nightmares involving the theme of separation; repeated complaints of physical symptoms when separation from major attachment

### Correspondence

Claudia Carmassi, Department of Clinical and Experimental Medicine, Section of Psychiatry, University of Pisa, via Roma 67, 56126 Pisa, Italy • Tel. +39 050 2219766 • Fax +39 050 2219787 • E-mail: ccarmassi@gmail.com

figures occurs or is anticipated. Besides deleting the age limitation, the DSM-5 requires that fear, anxiety, or avoidance last 4 weeks or more in children and adolescents, and at least 6 months in adults.

Prior to the introduction of the DSM-5 criteria, the literature in this field investigated adult Separation Anxiety Disorder generally using semi-structured interviews based on existing DSM-IV-TR criteria adapted to adulthood. Specific terms had, in fact, been adopted across different studies. Adult-onset Separation Anxiety Disorder refers, in fact, to an adult Separation Anxiety Disorder diagnosis without a documented history of childhood Separation Anxiety Disorder, whereas childhood-onset adult Separation Anxiety Disorder refers to an adult Separation Anxiety Disorder diagnosis in individuals who have also met the criteria of Separation Anxiety Disorder during childhood.

In adult patients, anxiety might focus on parents, but more often involves intimate partners and children<sup>7,8</sup>, with marked discomfort when separating from them<sup>1</sup>. While in children worries usually concern accidents, kidnapping and deaths, adults suffering from Separation Anxiety Disorder may also show difficulties in coping with changes in circumstances, such as moving or getting married<sup>1</sup>. Somatic symptoms that are usually prominent in childhood Separation Anxiety Disorder, such as nausea and stomachaches<sup>2</sup>, seem to be less frequent in adults who instead show more cognitive and emotional symptoms<sup>7</sup>. Moreover, as a way to deal with their fears and ensure a contact with attachment figures, adults with Separation Anxiety Disorder might make frequent phone calls, adhere to rigid routines or talk excessively.

Despite most youths suffering from Separation Anxiety Disorder are thought to make a good recovery through puberty and adult life<sup>1</sup>, the long-term outcome of childhood Separation Anxiety Disorder is actually not clear. Besides some studies identifying it as either a specific risk factor for adult panic disorder (PD)<sup>9</sup> or a general risk factor for multiple adult mental disorders<sup>10-12</sup>, growing clinical and epidemiological data have been showing that Separation Anxiety Disorder may also persist through adulthood. The available epidemiological data, in fact, indicate that the lifetime prevalence of Separation Anxiety Disorder in the general adult population ranges from 4.8 to 6.6%<sup>5,13</sup>. Moreover, despite the assumption that late onset is uncommon, many persons classified as having adult Separation Anxiety Disorder report first onset in adulthood<sup>13,5</sup>.

## Epidemiological and clinical data

Adult Separation Anxiety Disorder was first explored in clinical settings with prevalence rates ranging approxi-

mately between 20 and 40%<sup>14,15</sup>. Manicavasagar et al.<sup>14</sup> showed a prevalence of adult Separation Anxiety Disorder, assessed with the *Adult Separation Anxiety Symptom Questionnaire* (ASA-27), of 46% in patients with PD or generalised anxiety disorder. Consistently, in a large cohort of 508 outpatients with anxiety and mood disorders assessed by means of DSM-IV-TR criteria adapted to adulthood, a prevalence of adult Separation Anxiety Disorder was found to be as high as 42.4%, with about 50% of these latter cases reporting an adulthood onset of the disorder<sup>6</sup>. Silove et al.<sup>15</sup>, on a large sample of anxiety patients, reported an estimate prevalence of adult Separation Anxiety Disorder was 23%.

Two recent investigations also provide some epidemiologic data about Separation Anxiety Disorder. The National Comorbidity Survey (NCS-R)<sup>5</sup>, carried out on 5692 adults, found Separation Anxiety Disorder to be common in the US, as lifetime prevalence estimates of childhood and adult Separation Anxiety Disorder were 4.1% and 6.6%, respectively. Diagnosis was based on retrospective assessments using a criterion set parallel to that of the DSM-IV-TR<sup>2</sup>, "making age-appropriate modifications to the criterion A symptom questions". One third of childhood cases persisted into adulthood, while the majority of adult cases had first onset in adulthood. Moreover, Separation Anxiety Disorder was significantly more common in women than men, in people between 18 and 59 years, and in the never married and previously married (compared to the currently married or cohabiting). More recent data from the World Mental Health Surveys of the World Health Organization (WHO) show lifetime prevalence Separation Anxiety Disorder rates as high as 4.8% across Countries, with almost a half of lifetime onsets occurring after the age of 18<sup>16</sup>. Controlling for lifetime comorbid disorders, age and country, Separation Anxiety Disorder was significantly associated with being female, having low through high-average education, maladaptive family functioning childhood, other childhood adversities, and a variety of lifetime traumatic events. It is noteworthy that the associations between maladaptive family functioning, childhood adversities and other lifetime traumatic events predicted not only paediatric-onset, but also adult-onset Separation Anxiety Disorder.

Childhood Separation Anxiety Disorder is more common in girls with almost twice as much as the rates reported in boys<sup>16</sup>. Conversely, gender differences appear to be less strong in adult Separation Anxiety Disorder, despite females appear to be more symptomatic than men<sup>5,16,17</sup> and males are more likely to report first onset in adulthood<sup>5</sup>. Clinical studies are in line with these data. When comparing outpatients with anxiety and mood disorders with and without adult Separation Anxiety Disorder, higher

female/male ratios were found in those with than those without adult Separation Anxiety Disorder<sup>6</sup>. In addition, a study on early separation anxiety symptoms of adult patients with Separation Anxiety Disorder found elevated scores only in females<sup>15</sup>.

## Comorbidities with other mental disorders

Epidemiological investigations show that adult Separation Anxiety Disorder is highly comorbid with other mental disorders and is associated with substantial impairment in role functioning that persists even after controlling for comorbidity<sup>5</sup>. The WHO Mental Health Survey data also revealed significant time-lagged associations between Separation Anxiety Disorder and other disorders, including not only internalising disorders (e.g., major depression, bipolar disorder, specific and social phobias, PD, generalised anxiety disorder and/or post-traumatic stress disorder), but also externalising ones (e.g., ADHD, oppositional defiant disorder, and conduct disorder), supporting the hypothesis that Separation Anxiety Disorder represents a generic risk factor for a range of common mental illnesses. As for clinical samples, growing evidence shows that Separation Anxiety Disorder is common in psychiatric settings. Prevalence estimates ranging from 23% to 65% have, in fact, been reported among patients with mood and anxiety disorders<sup>6 15</sup>.

### Anxiety disorders

A close relationship between Separation Anxiety Disorder and PD has been consistently found in adult patients<sup>15 18-20</sup>. The relationship between Separation Anxiety Disorder and PD is still debated. Separation sensitivity is considered a dimension of PD and, therefore, it was included among the panic-agoraphobic spectrum symptoms<sup>21 22</sup>. On the other hand, the agoraphobic-like dimension of Separation Anxiety Disorder might enhance the comorbidity between this latter and PD, and raises doubts about its distinctiveness. However, researchers have pointed out the fact that Separation Anxiety Disorder often precedes the onset of other anxiety disorders, and postulated that panic attacks might be secondary to Separation Anxiety Disorder<sup>8 14 23</sup>. A recent meta-analysis<sup>19</sup> found that a childhood diagnosis of Separation Anxiety Disorder significantly increases the risk of PD and other anxiety disorders, confirming that this disorder may represent a vulnerability factor for mental illnesses.

### Mood disorders

People with adult Separation Anxiety Disorder show higher levels of depression even without high comorbidity rates with Major Depressive Disorder (MDD)<sup>6 15</sup>. In-

terestingly, Kossowsky's<sup>19</sup> meta-analysis confirmed that, after adjusting for publication bias, childhood Separation Anxiety Disorder is not associated with adult MDD. On the other hand, some investigations suggested a specific association between bipolar disorders (BD) and Separation Anxiety Disorder<sup>5</sup>. While Separation Anxiety Disorder has been demonstrated to be significantly more frequent in patients with BD type I and PD than those with MDD, a few data indicate a relationship between Separation Anxiety Disorder and mood spectrum symptoms. A strong correlation between Separation Anxiety Disorder symptoms and lifetime mood spectrum symptoms of both polarities was found in patients with complicated grief (CG) and in healthy controls<sup>24</sup>. Similarly, a significant association between lifetime mood symptoms and Separation Anxiety Disorder among subjects with CG, PTSD and PD has been reported<sup>25 26</sup>.

### Post-Traumatic Stress Disorder (PTSD)

In consideration of the fact that Separation Anxiety Disorder is characterised by intense anxieties and fears concerning separations from or harm to attachment figures, a growing interest has been recently devoted to the pattern of comorbidity involving Separation Anxiety Disorder, PTSD and pathological grief reactions. Some literature data have pointed out the possibility that traumatic events may precipitate Separation Anxiety Disorder in children and adolescents<sup>27 28</sup>. However, only limited data are available about possible associations between traumatic events and adult Separation Anxiety Disorder<sup>5 14 24 25 29 30</sup>.

Some evidence suggests that Separation Anxiety Disorder tends to co-occur with PTSD amongst adult populations exposed to traumatic losses and network-related traumas<sup>4 25 29</sup>. Silove et al.<sup>29</sup>, in a study exploring trauma-affected Bosnians resettled in Australia, showed that adult Separation Anxiety Disorder was strongly comorbid with PTSD, with almost all individuals with adult Separation Anxiety Disorder having comorbid PTSD, but not with traumatic grief. Moreover, among PTSD dimensions, adult Separation Anxiety Disorder was specifically linked to avoidance and hyperarousal, but not to re-experiencing. This association between Separation Anxiety Disorder and PTSD was also found in the NCS-R study<sup>5</sup> where PTSD was found to be one of the strongest pattern of comorbidity with adult Separation Anxiety Disorder among Axis I disorders. This led the authors to hypothesise that the intense personal insecurity might be the common factor underlying PTSD and adult Separation Anxiety Disorder<sup>29</sup>. In people with adult Separation Anxiety Disorder, this fear for personal safety may drive the need to maintain proximity to attachment figures, while in trauma-affected individuals it may in-

crease the likelihood of experiencing PTSD symptoms. Most recently, an analysis of the cross-national World Mental Health Survey dataset indicated that Separation Anxiety Disorder (assessed across the lifespan) was one of only a few prior disorders statistically associated with subsequent PTSD onset<sup>31</sup>, thus preceding and predicting it. Consistently, Tay et al.<sup>30</sup> found that adult Separation Anxiety Disorder symptoms play an important role in mediating the effects of traumatic losses and worry about family in the pathway to PTSD symptoms in 230 refugees from West Papua. In light of these data, the authors proposed an evolutionary model in which the adult Separation Anxiety Disorder and PTSD reactions may represent complementary survival responses designed to protect the individual and close attachments from external threats. In particular, separation anxiety in response to attachment threats could represent a mechanism activating PTSD symptoms through a pathway that may be intensified in the case of repeated threats to close others, as it happens in refugees. In support to this theory, the authors highlighted the evidence that both Separation Anxiety Disorder and PTSD reactions are mediated by neuronal substrates located in the amygdala, which is the brain center responsible for initiating the learned fear response<sup>4,32</sup>.

### **Complicated Grief (CG)**

In the past decades, a growing interest has been devoted to the distinction between normal and “pathological” grief processes, particularly complicated and traumatic grief, so that the DSM-5 acknowledged Persistent Complex Bereavement Disorder within the third section of disorders deserving further studies<sup>33-35</sup>.

Symptoms of CG may vary and include recurrent and intense pangs of grief, preoccupation with the deceased, recurrent intrusive images of the loved one and a strong desire to join their loved one that can lead to suicidal thoughts and behaviours<sup>34-36</sup>. In the DSM-IV-TR, bereavement was said to be likely present with symptoms of a MDD or PTSD only, this latter in the case of a traumatic death. Nevertheless, increasing data has highlighted grief not to be characterised by prolonged depression but acute and episodic “pangs”. Research data, in fact, has suggested its phenomenological closeness to separation anxiety rather than to depressive symptoms.

On the other hand, since Bowlby started his work on attachment<sup>37</sup>, separation and loss have always been treated together and attachment theory has offered insight into both separation anxiety and grief. In fact, some studies have reported a link between insecure attachment styles and both complicated grief<sup>38,39</sup> and Separation Anxiety Disorder symptoms<sup>37</sup>. Moreover, it has

been proposed that the exposure to a traumatic event, as a loss, may trigger symptoms associated with adult Separation Anxiety Disorder<sup>15,27</sup>; Vanderwerker et al.<sup>40</sup> reported that childhood Separation Anxiety Disorder is linked to a higher risk of developing complicated grief in adulthood.

The first study exploring adult Separation Anxiety Disorder among patients with CG found that these patients showed significantly higher scores on the ASA-27 with respect to healthy control subjects<sup>24</sup>. A later clinical study, aimed at comparing the clinical features of CG with those of patients with PTSD and with PTSD and CG in comorbidity, found that patients with comorbid PTSD and CG reported significantly higher ASA-27 scores compared to patients with one of the two disorders alone<sup>25</sup>. These data corroborated results from Silove et al.<sup>29</sup> who found adult Separation Anxiety Disorder to be associated with PTSD, but not with depression or CG among trauma-affected Bosnians resettled in Australia. Authors argued that the temporal focus of grief and Separation Anxiety Disorder may have accounted for this finding: the former constellation being past oriented, while separation-related anxieties are directed towards the present and future safety of attachments<sup>29</sup>. On the other hand, traumatic loss has been correlated with symptoms of Separation Anxiety Disorder. Boelen et al.<sup>41</sup> reported that prolonged grief disorder, MDD, and adult Separation Anxiety Disorder were better conceptualised as distinct dimensions instead of a unitary dimension of distress. Interestingly, the cause of loss was the single variable that was associated with all three symptom-clusters, with loss due to violent cause giving rise to more severe symptoms. Most recently<sup>20</sup>, some of us explored the prevalence and clinical significance of adult Separation Anxiety Disorder in a help-seeking sample of 151 adults with CG. Results showed adult Separation Anxiety Disorder to be highly prevalent among patients with CG and associated with greater symptom severity, greater impairment and more comorbidity with PTSD and PD.

It is noteworthy that recent studies have pointed out that the presence of adult Separation Anxiety Disorder affects treatment outcomes in patients treated with psychotherapy<sup>42,43</sup>. Yet based on these researchers’ findings, separation anxiety might be expected to act as a moderator of response to CG treatment in bereaved people.

## **Perspectives for future research**

### **Developing targeted treatment**

While currently included among anxiety disorders, Separation Anxiety Disorder has been considered for a long

time a childhood disorder, such that clinicians are still not fully aware of its prevalence, course and relevance during adulthood. The DSM-5 reformulation of Separation Anxiety Disorder therefore requires a paradigm shift in which clinicians are alerted to identifying and treating the condition in all age groups<sup>44</sup>. However, findings from clinical and epidemiological settings highlight that Separation Anxiety Disorder cause clinically relevant impairment, over and above the effect of concomitant mental disorders. Moreover, growing data are pointing out that the presence of Separation Anxiety Disorder plays a crucial role in moderating treatment outcomes of other comorbid disorders. Kirsten et al.<sup>43</sup> found that patients treated with cognitive-behavioural therapy for PD, social phobia, or generalised anxiety disorder were less likely to show reductions in anxiety and depression when having comorbid Separation Anxiety Disorder. Aaronson et al.<sup>42</sup> found that patients with PD treated with cognitive-behavioural therapy were significantly more likely to show a poor outcome if they had comorbid Separation Anxiety Disorder, even controlling for relevant clinical and demographical variables. More recently, Miniati et al.<sup>45</sup> showed that symptoms of separation anxiety are predictors of poor outcome in adults with PD under psychopharmacological treatment. These findings not only highlight the need of raising clinicians' awareness on Separation Anxiety Disorder, but should also prompt researchers to develop and test targeted treatments for adult patients.

### *Elucidating developmental pathways of separation anxiety disorder*

Notwithstanding the inclusion of Separation Anxiety Disorder among anxiety disorders mostly depended on the acknowledgement of childhood-onset cases persisting through adulthood, growing literature has also shown that Separation Anxiety Disorder might have an onset after puberty and virtually at any age. Therefore, the main challenge about DSM-5 Separation Anxiety Disorder is what may act as a trigger for the adult-onset of the disorder.

While a few studies have elucidated the clinical correlates of adult Separation Anxiety Disorder, no longitudinal studies have been undertaken to accurately evaluate if adult-onset Separation Anxiety Disorder may precede, follow, or come along with other mental disorders. Moreover, limited research has been conducted up to date aiming to investigate whether certain life events may precipitate Separation Anxiety Disorder symptoms during adulthood. However, it is noteworthy that Separation Anxiety Disorder has been found to be highly prevalent among subjects with PTSD and/or CG, and that lifetime traumatic predict adult-onset Separation Anxiety Disorder,

suggesting the hypothesis that some sort of life events, such as a personal threat or the loss of a close one, might trigger Separation Anxiety Disorder during adulthood. The potential value of a neurodevelopmental perspective for understanding aetiological factors in psychopathology has been recently highlighted<sup>46</sup>. Specifically, it has been pointed out that what have been traditionally considered to be distinctive forms of psychopathology may have common features or may represent age-adjusted variations of common underlying dispositions. This might easily fit the debated relationship between early-onset Separation Anxiety Disorder and anxiety disorders of adulthood. On the other hand, integrating such perspective with a vulnerability-stress-disease model, adult-onset Separation Anxiety Disorder may represent the late clinical manifestation of a latent vulnerability, interacting with specific, severe life events. Longitudinal, prospective investigations are warranted to elucidate factors associated with the onset of Separation Anxiety in adulthood with important preventive clinical implications.

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