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BJPsych Advances (2021), vol. 27, 145–152 doi: 10.1192/bja.2021.1

Stress-related physical and mental disorders: a new paradigm

ARTICLE

Uriel Halbreich

SUMMARY

Stress-related disorders are diverse and they may be mental and physical. Often, several body systems and organs are involved simultaneously. The pathophysiology of stress-related disorders involves many factors: an observable or perceived stressor, an individual dynamically evolving vulnerability and maladaptation leading to imbalance, as well as environmental, cultural, gender and life-cycle variables. There is a need to develop a comprehensive quantifiable stress assessment instrument. It would be based on the 'stress factor', a dimension that would integrate biological, psychological, social, economic and spiritual parameters and would allow for cultural sensitivity. It would contribute to clinical operational sophistication and would illuminate treatment options and multidimensional well-being interventions. Hopefully, it would facilitate development of culturally sensitive pharmaceutical or biophysiological adaptogens and homeostatic interventions.

LEARNING OBJECTIVES

After reading this article you will be able to:

- appreciate the importance of homeostasis
- demonstrate increased awareness of the consequences of stress
- delineate the physical and mental stress-related disorders.

KEYWORDS

Stress; trauma; mental disorders; physical disorders; diagnosis.

From a global perspective, stressful situations and events are everywhere. Some are natural disasters such as pandemics, floods, earthquakes and tsunamis, and some arise from human activity, such as terrorism, wars, migration, accidents, economic collapse or mismanagement of natural processes (Halbreich 2019). With the COVID-19 pandemic entering its second year, we have been confronted with at least two facts. First, infection in a specific region can spread to become a global pandemic of disastrous proportions. Second, the stress caused by the pandemic can effect more severe and broader socioeconomic and individual damage than the virus itself. Furthermore, anticipation of the seemingly unavoidable consequences of the stressful situation and their uncertainties takes its own additional toll and amplifies stress. Even though some individuals may be immune to the stressor, many are vulnerable to the consequences. Depending on the individual and their social, cultural and economic milieu, that vulnerability may be manifested as symptomatic pathology. Clinical symptoms may be emotional and/or physical.

The multitude and diversity of symptoms that may be induced by stressors calls for delineation of an interdisciplinary domain of stress-related disorders that would be pertinent to all symptoms, syndromes and disorders.

Stress-related disorders should be described and defined by stressor, timing and impairment. They are not defined by specific descriptive symptoms; rather, they might be a subtype of an established diagnosis or a pathway to the manifestation of a symptom. For instance, an acute increase in blood pressure may be caused by an acute stressor. That stressor might exacerbate higher blood pressure in people with arteriosclerotic hypertension or other cardiovascular disorders. Similarly, severe depression may occur and its symptoms may or may not meet ICD-11 criteria for major depressive disorder (World Health Organization 2018); they might be classified as a subtype of major depressive disorder, or eventually, if descriptive diagnosis evolves to pathology-based entities, they might be included in a cluster of stress-related disorders. In this case 'depression' would serve as a symptom that is a departure point for differential diagnosis, as is hypertension (Halbreich 2006). Certainly, such a diagnosis as a stress-related disorder would call for a stress-related treatment.

Terminology

Stress

The concept of stress and its consequences have been widely discussed, especially from a research perspective (e.g. Koolhaas 2011). In this article I consider stress and stress-related disorders from a holistic perspective, relevant to clinical practice. I would suggest that almost any symptom, mental or physical, may be stressor related. The ICD-11 criteria can serve as a departure point, but they could

Uriel Halbreich, MD, is Professor of Psychiatry and Director of Bio-Behavioral Research at Jacobs School of Medicine and Biomedical Sciences, University of Buffalo, State University of New York (SUNY-AB), USA. He is Founding Chair of the World Psychiatric Association (WPA) Section on Interdisciplinary Collaboration. His research embraces the biology of affective disorders and the development of biological markers and clinical laboratory tests for major depressive disorder, and hormonal modulation of brain and behaviour via gonadal hormones and hypothalamic–pituitary–adrenal system neurotransmitters and their metabolites.

Correspondence Uriel Halbreich. Email: uhalbreich@gmail.com

First received 8 Sep 2020
Final revision 9 Dec 2020
Accepted 11 Jan 2021

https://doi.org/10.1192/bja.2021.1 Published online by Cambridge University Press

be expanded beyond mood and cognition to include any organ or system. The emphasis should be on etiology and pathophysiology and not just on the descriptive symptom.

Formally, ICD-11 includes a category of 'Disorders specifically associated with stress', in the chapter on mental, behavioural and neurodevelopmental disorders (World Health Organization 2018). Entities in this section are directly related to exposure to a stressful or traumatic event, or a series of such events or adverse experiences. For each of the disorders in the grouping, an identifiable stressor is a necessary although not sufficient causal factor. The description notes that, although not all individuals exposed to an identifiable stressor will develop a disorder, the disorders in the grouping would not have occurred without experiencing a stressor. Stressful events for some disorders in this grouping are within the normal range of life experiences, for example divorce, socioeconomic problems and bereavement. Other disorders require the experience of a stressor of an extremely threatening or horrific nature – potential traumatic events. It is the nature, pattern and duration of the symptoms that arise in response to the stressful events, together with associated functional impairment, that distinguishes the disorders. They include post-traumatic stress disorder (PTSD), complex PTSD, prolonged grief disorders, adjustment disorder, reactive attachment, disinhibited social engagement and the like. In another chapter, ICD-11 describes 'Acute stress reaction', under the parent definition 'Problems associated with harmful or traumatic events'. The 'problems' or consequences may be clustered as the descriptively diversified stress-related disorders. Their basic criteria are delineated in Box 1.

Stressors

The definition of a stressor might be subjective. In many cases, events are so disastrous that a cause for stress is obvious to most observers. However, even events that are considered in psychiatric literature to be traumatic, such as combat, may be exhilarating to some individuals. It has been suggested (Selye 1956; Crum 2017) that a 'stress mindset' may shape an individual's response to a given event. People who consider a crisis to be an opportunity and not a stressful threat demonstrate a better adaptational physiological response, which may be an increase in arousal of the sympathetic nervous system and suppression of the parasympathetic system. Therefore, a stressor might be defined as any event, situation or environmental condition that is subjectively perceived as having a negative impact on the individual. Maladaptive stress occurs if the required response exceeds the adaptive capacity of the organism and causes distress (Selye 1976).

Clinically, I suggest defining stress as 'a subjective feeling of inadequacy and inability to cope'. This definition might be expanded to 'an expression of maladaptation of an individual or a system'. This is compatible with a suggested concept (Koolhaas 2011) that 'most activities of a living organism directly or indirectly concern the maintenance of a homeostasis, an optimal set-point (e.g. blood pressure, glucose) or balance'. Accordingly: a stressor is any perturbation from the outside world that disrupts homeostasis (Selye 1959; Sapolsky 1992). It might also be of internal origin, as with pain.

Homeostasis

Homeostasis (Cannon 1932) is a dynamic physiological and emotional balance of the body's multiple systems that maintains optimal functioning. The balance requires continuous adaptation to external and internal changes. Bruce McEwen introduced the concept of allostasis, which is the brain process for maintaining a normal range of brain–body functions (McEwen 1993). When changes are very substantial or too rapid, they may challenge homeostasis and provoke a need for extra physiological effort of adaptation. This may be perceived as stress.

When the acute challenge is over, the body should return to a baseline homeostatic balance. However, if challenges or stressors are too severe or too frequent, or adaptational mechanisms are impaired and not well-orchestrated, a chronic abnormal imbalance may ensue and contribute to wear and tear in the body's systems – an 'allostatic load' – which may result in chronic symptoms and disorders. McEwen also introduced the concept of 'allostatic overload', in which imbalance is chronically non-restored and leads to chronic disorders such as chronic hypertension or accumulation of abdominal fat (McEwen 2003, 2020). Acute adaptations may be advantageous in the short term but

BOX 1 Stress-related disorders: defining principles

- There should be an identifiable or perceived stressful event or situation
- Symptom(s) or disorders appear or are exacerbated following the stressor
- Specific symptoms may be emotional, cognitive and/or physical (depending on individual vulnerability and sociocultural context)
- There is self-reported or observed impairment in daily life, family or social functioning and/or functioning of body systems
- Timing may be acute or chronic

BJPsych Advances (2021), vol. 27, 145–152 doi: 10.1192/bja.2021.1

deleterious in the long term (McEwen 1998, 2003, 2011, 2020). Although stress does have positive aspects (Selye 1956) I will focus on the negative aspects, in particular acute and chronic stress disorders.

For research purposes the distinction between 'acute' and 'chronic' still needs to be precisely delineated. For clinical practice we consider an acute stress response to be the immediate impact of any stressor. Chronic stress is a continuous disorder that may start in response to an acute event or as a consequence of a continuous stressful situation.

Defining a stressor as a disruption of homeostasis implies that stress is associated with or might cause an imbalance in the delicate dynamic physiological processes that maintain healthy functioning. Optimally, balance is maintained and restored by brain–body adaptational mechanisms. When adaptation fails or is too costly to the individual's body, a disorder develops. The main pathophysiological mechanisms leading to stress-related disorders are delineated in several articles in this issue of *BJPsych Advances*.

Repeated stressful insults, continuous distress or continuous response to an acute stressor when such a response is no longer necessary for an optimal adaptation might result in a biological 'wear and tear' or allostatic load (McEwen 1998, 2011) and a chronic stress-related disorder. Therefore, we may operationalise the multidimensional construct of stress-related disorders to include consequences of any adverse event or situation that is perceived as stressful. Symptoms may be diverse and multiple, mental and physical, acute or chronic.

Optimally, treatment should be aimed at stress reduction and restoration of balance.

The need to quantify stress: developing the concept of the stress factor

'Stress' is a broad concept. It varies from positive to negative, from a productive challenge to a trauma, from mild to extremely severe disorder, even death. Its expressions are various and may affect any body system, from head to toe. Therefore, it has to be quantified to provide practical utility for investigators and clinicians.

Considering the diversity of physical and mental diagnoses in ICD-11 to which stress may contribute and considering the proposed overlap among them, a general numerical indicator of stress would be of substantial clinical utility.

A departure point for demonstration of overlap and a common denominator among many current mental disorders is the story of elevated cortisol levels (Sachar 1970) and the dexamethasone suppression test (DST) (Carroll 1981) in patients diagnosed with major depressive disorder. Following initial excitement about biological markers and a possible test for major depressive disorder, it was shown that sensitivity is quite low – abnormalities of the hypothalamic–pituitary–adrenal (HPA) system are found only in a subgroup of patients. Specificity is even lower: with few exceptions, non-suppression in the DST was reported in many mental disorders based on observable or reported symptoms (Halbreich 1987). The diagnostic ramifications of these wide-spread cortisol abnormalities have not yet been incorporated in subsequent formal diagnostic nomenclature.

The need to re-evaluate associations among mental disorders and syndromes has been further corroborated more recently. It was noticed in epidemiological surveys that people who were diagnosed with a specific mental disorder tended to be diagnosed with many other mental disorders (Kessler 2011), which were initially interpreted as 'comorbidities'. A general factor of psychopathology was proposed to reflect this finding (Lahey 2011) and labelled the p factor. Its validity was demonstrated in genetic studies (Caspi 2013; Caspi 2018) as well as in large-scale population registers (Pettersson 2020).

Furthermore, the prevalence of mental symptoms among people with diverse physical disorders, as well as the prevalence of physical adverse effects of psychotropic medications (Halbreich 2000), may suggest common denominators among some mental and physical phenomena and disorders. A search for such a common pathophysiology may take into consideration stress and its consequences. Ideally, each component of the stress response would be quantified, followed by a summary score.

How might we quantify the stress factor?

The process of development of a numerical score of stress – of quantifying the stress factor – might follow the example of the general intelligence score (the g score). At the turn of the 20th century, almost 120 years ago, it was noticed that the available intelligence scales overlapped each other. Suggestions to combine them and express 'general intelligence' as a single overall number (Spearman 1904) have since been widely accepted. A similar logic underlines the p factor and would be followed for the stress factor.

The process would commence with an 'objective' commonly accepted assessment of the stressor, the severity of the crisis, disaster or situation. This would be followed by attempt at quantification of the severity of the subjective perception of the

event/situation. The individual's history of life events and the positive or negative impact of these is important, as are the family history of stressful events and exposure of previous generations (Yehuda in this issue). The scope of current physical and mental symptoms and their severity should be documented and quantified, as should the severity of components and feelings of stress, including uncertainties, perceptions of unpredictability and lack of control. The individual's assessment of coping with the stress should be ascertained by assessment of impairment in daily life. Timing of symptoms in relation to the stimulus and their duration are also of importance.

The weight of each of the components would be studied on the way to a comprehensive numerical score.

The elaborate development of a scientific evidence-based instrument is lengthy and would be refined with accumulation of data. Eventually, presumed biological parameters would be studied and incorporated into the assessment if confirmed. Even before the stress factor measure and its procedures have been fully developed, clinicians should ask patients about each of the described components and arrive at a clinical impression.

Use of the stress factor in clinical practice

When established, the stress factor may initially supplement current diagnoses and provide for the option of treatment with stress-reduction procedures. Awareness of the stress factor among practising clinicians would improve treatment outcomes. Currently, patients are symptomatically treated according to their complaint and point of entry for treatment seeking; however, the knowledgeable clinician suspecting a stress-related disorder would investigate the trigger of their symptoms and underlying pathophysiology and refer patients for additional tests, assessments and consultations according to the probable cause. The stress factor would hopefully help in differential diagnosis of common conditions such as cardiovascular and metabolic disorders. Eventually, the associations between the various 'comorbidities' and the stress factor as their common denominator might lead to reconceptualisation and restructuring of diagnoses according to underlying processes of pathophysiology.

Mechanisms and consequences of stress

Hans Selye, the modern pioneer of understanding of stress, actually echoed concepts pursued by ancient Greeks and medieval Muslim healers. They were summarised and conceptualised by the 12th-century physician and philosopher Maimonides (1135–1204), who influenced pre-Renaissance thinking. Interestingly, his perception of health is quite similar to traditional Chinese ideas as well as current World Health Organization thinking. All may be distilled into two concepts: balance and adaptation.

A healthy state is described as a state of balance and equilibrium, and its disruption results in pathology. Selye suggested two general situations of health, balanced and imbalanced (or disordered). Accordingly, the first step in the diagnosis of stress-related disorders may be the determination of an imbalanced state (Selye 1959). It is still not clear what might be a biological marker of an imbalanced state, although Selye (Selye 1976) and many others suggested abnormalities of cortisol and adrenaline. Clinically, depression, which is prevalent in many stress-related disorders, may be suggested as an indicator of an imbalance. However, targeted studies are needed to confirm this possibility. Specific symptoms may be expressed according to individual vulnerability, context, environmental and cultural milieu, gender and the specific stage in the life-cycle.

The physiological mechanism of maintaining balance or homeostasis is still intriguing. There is a wealth of rapidly accumulating data on biological consequences of stress, and there is a good data-based understanding of balanced functions of hormonal systems and their disruptions. Most probably, neuroendocrinology plays a substantial role in healthy adaptation to stressors (Halbreich 1987; Dantzer 2020). However, to my knowledge a central mechanism of maintaining a comprehensive brain–body dynamic functional balance is still to be demonstrated and confirmed.

Stress-related disorders, syndromes and symptoms

It should be emphasised again that stress may cause, trigger, exacerbate or worsen almost any mental or physical symptom, with very few exceptions. Some examples are delineated below and a non-comprehensive list appears in Box 2.

Some brain-related (CNS) symptoms

It may well be assumed that the main organ of stress is the brain – the central nervous system (CNS) (McEwen 2006a, 2011). The brain is involved on two levels: (a) the cognitive perception of an event as stressful, pleasant, exciting or disturbing, and (b) the triggering of structural and physiological changes in response to the stressful event. It might be that the feelings of depression commonly associated with stress are related to the CNS changes.

Migraine is an example of a CNS-related disorder: it might be triggered by stressors and then grow in

BJPsych Advances (2021), vol. 27, 145–152 doi: 10.1192/bja.2021.1

BOX 2 Some stress-related disorders: systems and symptoms

- Brain: neurological, neurodevelopmental, emotional and cognitive expressions, e.g. post-traumatic stress disorder, adjustment disorders, depression, anxiety, sleep disorders, premature dementia, migraine headache, neck and shoulder pain
- Cardiovascular disorders, e.g. hypertension, cardiac arrest, stroke
- Metabolic disorders, e.g. diabetes (type 1 and type 2)
- Autoimmune disorders, e.g. multiple sclerosis, lupus erythematosus
- Asthma, allergies
- Obstetric and gynaecological problems and sexual dysfunction, e.g. fertility problems in women and men, menstrual cycle abnormalities, premenstrual syndrome, decreased libido, erectile dysfunction
- Stress during pregnancy – consequences for the baby
- Cancers and their treatments
- Dermatological conditions, e.g. acne, eczema
- Gastrointestinal and eating disorders, e.g. weight gain, obesity, constipation, irritable bowel syndrome
- Decreased immunity
- Increased vulnerability to infections

severity and frequency to become a stressor in itself, causing allostatic load and turning out to be chronic (Borsook 2012). Migraine is associated with changes that are also observed in other stress-related disorders, for example insulin resistance and elevated levels of glucagon-like peptides and leptin, thus showing some overlap with stress-related diabetes mellitus and severe major depressive disorder.

Similarly, sleep deprivation may be caused by stressors but then may become a stressor contributing to increased allostatic load and chronic stress (McEwen 2006b). It may be associated with increased evening cortisol levels ('flat cortisol curve'), elevated blood pressure and hyperinsulinaemia, as well as elevated levels of glucagon-like peptides and leptin.

Fibromyalgia may be a model for several chronic pain conditions that may be exacerbated by environmental factors such as barometric changes and may become a state of chronic pain and fatigue that causes additional allostatic load and stress (Martinez-Lavin 2009; Mukamal 2009).

Impact of stress during gestation and early development

Early-life stressors may programme stress circuits, producing alterations in neuroendocrine phenotypes and subsequent maladaptation, resulting in susceptibility to disorders or in altered responses to treatments (Markham 2010). Early-life stressors affect brain regions involved in cognitive and affective functions (frontal regions), feelings and emotions (the amygdala), thus further increasing vulnerability to any stressors in later life stages (Pechtel 2010). These reports emphasise the importance of perinatal and infant environments and atmosphere to the person's entire life. They extend on the many reports that any stress in the pregnant mother may cause disorders in her fetus and long-term disorders in her future offspring. This was demonstrated as early as the 1990s, when the British physician and epidemiologist David Barker noticed that cardiovascular disorders and metabolic syndromes were more prevalent among 40- to 50-year-old offspring of Dutch women who had been pregnant during the 'great famine' (1944–1945) towards the end of the Second World War (Barker 1993). Since publication of the 'Barker hypothesis', maternal stress has been demonstrated to have an impact on child development and behaviour and to result in several mental disorders later in life. The nature of the disorder may depend on the stage of the mother's pregnancy, suggesting that brain vulnerability may change over time (Bick 2015).

Brain vulnerability to stress is also manifested in later life. It has been suggested that people who reported repeated stressful life events or chronic stress aged more rapidly and tended to develop earlier dementia. It is still not completely clear whether this is attributable to cardiovascular disorder, structural or physiological mechanisms; most probably all are involved (Gilhooly 2016). High cortisol exposure over the lifetime, which is considered to be a consequence of repeated and chronic stress, has been reported to be linked to Alzheimer's disease and cognitive dysfunction, short-term memory loss and mild cognitive impairment (Lupien 2009; Khalsa 2015). Telomerase activity and length of telomeres (the protective caps of chromosomes) have been reported to reduce in response to acute psychological stress and even more so in chronic stress (Epel 2010).

Coronary heart disease and stroke

A recent report (Harris 2020) reminds us that people with ischaemic cardiomyopathy are at increased risk of substantial increase of diastolic blood pressure in response to a mental stress. It is well established that acute and chronic stress of any kind severely affect the cardiovascular system and may cause acute myocardial infarction, stroke and other consequences of damage to the system. This association has been demonstrated in numerous economies

and cultures and it appears to be global (Rosengren 2004; Steptoe 2012, 2013; O'Donnell 2016; Esler 2017; Kronenberg 2017). History of depression, psychosocial stressful events and long working hours appear to increase the risk of stress-related stroke and myocardial infarction (Rosengren 2004; Kotlega 2016, Kivimäki 2015).

Activation of the sympathetic nervous system, increased activity of the HPA system, decreased vagal nerve tone and increased coagulation in individuals with atherosclerotic vessels were all to be blamed (Mittleman 1995; von Känel 2001, 2015).

Diabetes mellitus

As mentioned above, Barker noticed that offspring of Dutch women who were pregnant during the 'great famine' of 1944–1945 had higher prevalence of cardiovascular disorders in middle age; he also found higher prevalence of type 2 diabetes mellitus (Barker 1993). The association between cardiovascular disorders and diabetes will not be elaborated here but it is quite established (Hales 2001). Furthermore, it has been established that stress, depression and other mood disorders may be associated with insulin resistance. Disruption of insulin metabolism may be influenced by gender, age, hormonal status as well as anthropological factors (Ely 2011). Therefore, individual vulnerability to exacerbation of diabetes or need to adjust diabetes management in stressful events and situations need to be carefully assessed.

Asthma and allergies

As is the case with many disorders, vulnerability to asthma may start *in utero*, as stress of the pregnant mother may cause respiratory hypersensitivity in the child. Early child abuse may further contribute to susceptibility to stress-induced respiratory problems (Romans 2002), as does air pollution (Exley 2015). Disrupted immune regulation in stressful situations and during episodes of depression is well documented (Marshal 2000; Frieri 2015). Further discussion is included in another article in this issue (Ravi *et al* in this issue).

Fertility in women and men

Stress affects many aspects of well-being throughout life-cycle, from gestation to old age. It should be noted that its impact starts even before conception, by influences on sperm and ovulation.

It is quite well established that women who seek treatment for infertility or pregnancy problems should be treated for stress reduction. It is less common that the male partners undergo similar interventions. It is of interest that men in stressful occupations or in stressful environments father more girls than boys. Un-published observations suggest that this is the case also during 'positive' stress. For instance, it was observed that Israeli combat pilots had mostly female offspring. A similar female:male ratio was observed in the Israeli border area near the Gaza strip during periods of bombing and rocket attacks. It is attributed to the fact that the Y chromosome is more vulnerable than the X chromosome, giving advantage to girls. This observation needs to be systematically documented and biologically confirmed, but the clinical ramification is quite clear: in cases of infertility, both partners may benefit from stress reduction.

Conclusions

To paraphrase on Selye's statement (Selye 1956) on stress, well-being comes first, everything else is just that – else. Accepting that 'normal' good health is a state of balanced harmony and capable adaptation, then balanced well-being is the optimal state of being. Its disruption pushes us to the negative side – 'the rest'. That is a consequence of stress.

Stress can disrupt all aspects of well-being. It challenges adaptation and may trigger imbalance and instability. The expressions of disruption are diverse and may involve different systems. An individual's symptoms may depend on genetic and epigenetic vulnerability, cultural and environmental context, gender and stage in the life-cycle. It may be intriguing to suggest that there may be an overall indicator of 'disordered balance' or dysregulation, which is then followed by specific symptoms. That indicator is currently still undetermined: clinically, it might be suggested that it is depression, which is prevalent in most stress-related disorders, or another, currently 'non-specific', symptom.

A general stress factor would be of clinical utility. It might supplement diagnoses and it might differentiate among subtypes of process-derived diagnoses and among similarly apparent symptoms and syndromes, thus assisting in treatment decisions. In patients with multiple diverse symptoms it would facilitate gaining access to treatment, preferably by an interdisciplinary integrated team.

The stress factor and its components would emphasise stress as a risk factor for various disorders in which the clinician should inquire about possible stressors and other life events. The delineation of the impact of stress should influence treatment decisions. Currently there are no Western medical modalities that are aimed at restoration of balance, although there are several effective interventions to restore balance within specific hormonal systems or to eliminate excessive fluctuations. Several non-Western techniques have been shown to be quite effective, such as acupuncture,

BJPsych Advances (2021), vol. 27, 145–152 doi: 10.1192/bja.2021.1

mindfulness and some herbal preparations. Cognitive–behavioural modalities to enhance predictability, reduce uncertainties and strengthen the individual's sense of being in control are already being developed. Pharmaceutical or biophysiological adaptogens and homeostatic interventions are still awaiting development and clinical trials.

In the current market-driven reality there is a need to (a) demonstrate the validity and prevalence of stress-related disorders and (b) pursue a clinically relevant paradigm shift from 'too little or too much' pathophysiological interpretations and treatment modalities to the investigation of 'multisystem balance and pursuit of adaptation'.

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

None.

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MCQs

Select the single best option for each question stem

1 Diagnosis of a stress-related disorder requires:

a a reported crisis/trauma
b that symptoms commenced following the crisis/trauma
c impaired functioning
d physical and mental examinations
e all of the above.

2 For assessment of a newly depressed patient, it is essential to:

a inquire about recent life events
b order blood tests for cortisol, noradrenaline and serotonin
c inquire about diet and exercise
d interview family/friends
e refer for a relaxation therapy.

3 Which of the following is not thought to be stress related?

a hypertension
b low birth weight
c muscular degeneration
d male infertility
e migraines.

4 The offspring of a pregnant woman physically abused by her husband are at increased risk of:

a becoming obese
b being born with bruises
c being born prematurely or with low birth weight
d being born with deformations
e intellectual disability.

5 What is not usually necessary for adequate adaptation to stressful situations?

a sense of control
b feeling of certainties
c bank account
d predictability of events
e optimism.

BJPsych Advances (2021), vol. 27, 145–152 doi: 10.1192/bja.2021.1