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CLINICAL CHARACTERIZATION OF ALLOSTATIC OVERLOAD

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Abstract

Allostatic load reflects the cumulative effects of stressful experiences in daily life and may lead to disease over time. When the cost of chronic exposure to fluctuating or heightened neural and systemic physiologic responses exceeds the coping resources of an individual, this is referred to as “toxic stress” and allostatic overload ensues. Its determination has initially relied on measurements of an interacting network of biomarkers. More recently, clinical criteria for the determination of allostatic overload , that provide information on the underlying individual experiential causes, have been developed and used in a number of investigations. These clinimetric tools can increase the number of people screened, while putting the use of biomarkers in a psychosocial context. The criteria allow the personalization of interventions to prevent or decrease the negative impact of toxic stress on health, with particular reference to lifestyle modifications and cognitive behavioral therapy.

Key-words: allostasis; allostatic overload; biomarkers; clinimetrics; life events; toxic stress.

1. The concept of allostatic load

In 1993, McEwen and Stellar (McEwen and Stellar, 1993) proposed a formulation of the relationship between stress and the processes leading to disease based on allostasis, the ability of the organism to achieve stability through change. The concept of allostasis emphasizes that healthy functioning requires continual adjustments of the internal physiological milieu. In response to environmental demands, different physiological systems interact with different levels of activity. The allostatic load is the cost of chronic exposure to fluctuating or heightened neural or neuroendocrine responses resulting from repeated or chronic environmental challenge that an individual reacts to as being particularly stressful (McEwen and Stellar, 1993). It refers to the wear and tear that results from either too much stress or from inefficient management of allostasis (McEwen, 1998, 2007). The definition of allostatic load reflects the cumulative effects of experiences in daily life that involve ordinary events as well as major challenges and also includes the physiological consequences of the resulting health damaging-behaviors, including poor sleep and other aspects of circadian disruption, social isolation, lack of exercise and poor diet. Indeed, major life changes are not the only source of psychological stress and physiological and neurobiological dysregulation. Because of adopting those health-damaging behaviors, subtle and long-standing life situations should not too readily be dismissed as minor or negligible, since chronic, daily life stresses may be experienced by the individual as taxing or exceeding his/her coping skills (Wagner, 1990). These aspects were often overlooked in conventional thinking about “stress”. The totality of external conditions in our lives, including our physical and social environments, called the “exposome” (Miller and Jones, 2014), determines what we do in making choices and influences our health-promoting and health-damaging behaviors. In particular, income inequality and increased social instability is an exacerbating factor leading to allostatic overload (Marmot and Wilkinson, 2006; Wilkinson and Pickett, 2010; Miller and Kirschbaum, 2018,).

As a result of experiences that lead to allostasis and adaptation but also to allostatic load and overload, the brain is changing its circuitry and function epigenetically (McEwen, 2017a, 2017b). “Adaptive

plasticity" refers to the fact that the brain remodels itself to help individuals handle the reality of their exposomes (McEwen et al., 2015, 2016). A key result of stress is structural remodeling of neural architecture, involving many cellular and molecular processes from the cell nucleus to the cell surface, leading to successful adaptation; whereas persistence of these changes when stress ends indicates failed resilience (Goldwater et al., 2009; Gray et al., 2014; McEwen et al., 2015, 2016; McEwen, 2017b).

The normal allostatic response is initiated by a stressor, sustained for an appropriate interval, and then turned off (McEwen, 2007). The threshold between tolerable stress (a physiological state that could potentially be disruptive but is buffered by the personal and interpersonal resources of the individual and occurs within a time-limited period) and toxic stress (strong, frequent, and/or prolonged activation of the body stress response system in the absence of buffering factors/protection) does not lend itself to an easy distinction (Shonkoff et al., 2009). McEwen and Wingfield (2010) defined allostatic overload as the transition to this extreme state.

Romero et al. (2009), in their Reactive-Scope model, use "homeostasis" instead of "allostasis" and assess reactions to the predictable circadian variation (predictive homeostasis) and responses to unexpected events (reactive homeostasis) as well as "homeostatic overload" and "homeostatic failure", which gets at the same idea as allostatic overload in response to toxic stress. Despite using different terminologies, the current version of the allostatic load model (McEwen, 2017a, 2017b) and the Reactive Scope Model (Romero et al., 2009) address the same issues of how experiences affect health over the life course. Of particular importance is promoting a healthy life trajectory (Halfon et al., 2014) with positive experiences involving reward (Dutcher and Creswell, 2018) and a sense of meaning and purpose in life (Fredrickson et al., 2013; Fava and Guidi, 2019). Figure 1 outlines the interacting mechanisms of allostatic overload.

2. Measurement of allostatic load

There have been several attempts to identify allostatic load by the use of its biological markers (Seeman et al., 1997, 2001; Gruenewald et al., 2006; Ryff et al., 2006; McEwen, 2007, 2015, 2017a, 2017b; Romero et al., 2009; Shonkoff et al., 2009; McEwen and Wingfield, 2010; Buckwalter et al., 2016; Wiley et al., 2016; Robertson et al., 2017; Mocayar Maron et al., 2019). The biological model of allostatic load focuses on glucocorticoid dysregulation as part of a network of mediators involving autonomic, endocrine, metabolic, and inflammatory parameters (McEwen and Stellar, 1993; Seeman et al., 2001). It has been expressed in a cumulative index encompassing a battery of biomarkers such as: resting systolic and diastolic blood pressure, body mass index, waist-hip ratio, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, fasting glucose, plasma C-reactive protein, fibrinogen, serum measures of interleukin-6, the soluble adhesion molecules E-selectin, intracellular adhesion molecule-1, levels of urinary epinephrine, norepinephrine, cortisol and a serum measure of the hormone dehydroepiandrosterone sulfate (DHEA-S) (Seeman et al., 2001). This index of allostatic load was found to be better predictor of mortality and decline in physical functioning than individual biomarkers alone, yet a number of limitations emerged due to the complexity and dynamic nature of this multisystem network (Buckwalter et al., 2016).

A state of allostatic load entails some clinical manifestations that can be observed in daily practice. Examples may be provided by worsening of symptoms during weekends or vacation (inability to shut off responses associated with lack of distraction entailed by work), or breakdowns that occur just when a stressor has terminated (caregivers of patients successfully recovering after a long struggle). Help in determining a state of allostatic overload and in getting at the underlying experiential factors that may accelerate disease processes may come from clinimetrics, the science of clinical measurements (Feinstein, 1987; Fava et al., 2012, 2018). The term “clinimetrics” was introduced by Alvan R. Feinstein in 1982 (Feinstein, 1982) to indicate a domain concerned with indices, rating scales and other expressions that are used to describe or measure symptoms, physical signs and other clinical phenomena, which do not find room in the customary taxonomy (Feinstein, 1987; Fava et al., 2012, 2018).

Clinimetric criteria for the determination of allostatic overload have been introduced in 2010 (Fava et al., 2010). A slightly revised version, incorporated in the Diagnostic Criteria for Psychosomatic Research (DCPR), was published in 2017 (Fava et al., 2017).

3. Clinimetric definition of allostatic overload

The criteria for the determination of allostatic overload (Fava et al., 2017) that can be used in clinical practice (Table 1) are based on insights derived from psychosomatic research.

The first point (Table 1, A) deals with the specification of the stressor. The notion of contextual threat (the judgement of the expected stressfulness of the event, when its full nature and particular circumstances are taken into account) has been important in medical and psychiatric disorders (Brown and Harris, 1986; Paykel, 1997). On the one hand, uncontrolled and undesirable events have been identified as the most threatening challenges, particularly when they are events of major importance to the patient and result in major changes in patient's living conditions, social and family circle, and work. Examples are the loss of a significant person, acute medical illness, separation, relocation, etc. On the other hand, subtle and long-standing life situations, such as those occurring at work or dealing with a chronic illness, may be experienced by the individual as taxing or exceeding his/her coping skills. Thus, both life events and chronic stresses can constitute a source of allostatic load.

The second point in the criteria (Table 1, B) is concerned with the clinical manifestations, which may encompass psychological symptoms, impairment in social and occupational functioning and in psychological well-being, mainly in the form of environmental mastery (Ryff et al., 2006; Fava, 2016).

Determination of the presence of allostatic overload requires careful exploration of patient's life circumstances. The semi-structured interview that has been developed for diagnosing allostatic overload (Fava et al., 2010, 2017) is shown in Table 2. Assessment of life events by a detailed interview method, such

as the Interview for Recent Life Events (Paykel, 1997), is certainly the gold standard, but it is time consuming and unsuitable for a busy practice. A generic question about anything that happened recently entails the risk of missing both important life events and chronic stress (Paykel, 1997). The Psychosocial Index (PSI) (Sonino and Fava, 1998; Piolanti et al., 2016) is a short clinimetric index, tailored to a busy clinical setting, for the assessment of stress and related psychological distress (allostatic load). Items of the questionnaire served as a basis for the semi-structured interview (Table 2).

All this information may help formulating a global clinical judgement of an individual's assets and coping skills in dealing with his/her current life situation. Unlike in the case of adjustment disorders in DSM-5 (American Psychiatric Association, 2013), the presence of a psychiatric disorder is not a source of exclusion from the criteria. The category of adjustment disorders in DSM has displayed major conceptual and methodological flaws (Semprini et al., 2010; Bachem and Casey, 2018). A major problem is the fact that it is an exclusion diagnosis (it cannot be applied in comorbidity with other psychiatric disorders) and overlaps with subthreshold manifestations of mood and anxiety disorders. Allostatic overload is a trans-diagnostic categorization that may be applied regardless of the presence of psychiatric and/or medical conditions.

4. Advantages of the clinimetric evaluation of allostatic overload

The clinimetric evaluation of allostatic overload has some major advantages compared to other stress-related models. Indeed, classic models analyze individual components of the stress response separately. For example, Holmes and Rahe (1967) focused on identifying major life events with the assumption that, although not impactful all the same, life events still exert identical adverse effects on everyone. Their approach is however limited by their inability to recognize the role that individual's resources and cognition play in the stress response.

Lazarus and Folkman (1984) addressed this problem with their model of cognitive appraisal. Accordingly, it is not the event per se to cause distress, but its evaluation by the person (e.g., beyond his/her coping abilities). While emphasizing the contribution of the cognitive component to the stress response, Lazarus and Folkman (1984) failed to include the influence of the physiological response to stress. Indeed, individuals with high sensitivity to stress may have an altered physiological response that, in turn, negatively impacts people's ability to conduct a successful appraisal of the situation.

Classic models focusing on the physiological response to stress, such as Cannon's (1932) and Selye's (1956), discounted the role of cognition in modulating this response. Indeed, although all stressors determine the activation of the same circuits with a partial suppression of the parasympathetic system and arousal of the sympathetic one, people with a mindset considering stress as an opportunity for growth more, than a threat, have a more adaptive physiological response (Crum et al., 2017).

The clinimetric evaluation of allostatic overload overcomes the limitations of the classic models and answers the question: "When can we consider an individual as clinically stressed?"

Criterion A (Table 1) focuses on the stressors. Careful choice of stressful life events avoids the confounding of events with psychiatric symptoms, a problem that has long been recognized as a limitation of commonly used scales (Dohrenwend et al., 1984).

Criterion B (Table 1), including psychosocial and physical symptoms, embraces both the physiological and cognitive components of the stress response (Figure 1).

5. Clinical use of criteria for allostatic overload

Clinimetric criteria have been used in a number of studies.

General population. A first investigation was carried out in the general population (Tomba and Offidani, 2012). Patients who were identified as presenting with allostatic overload displayed significantly

higher scores at the PSI self-rated stress, distress and abnormal illness behavior (Sonino and Fava, 1998; Piolanti et al., 2016) and at the Clinical Interview for Depression (CID) total score (Paykel, 1985; Guidi et al., 2011) than subjects who did not present with allostatic overload (Tomba and Offidani, 2012). The results showed that the clinimetric criteria for allostatic overload, merging different information otherwise assessed by several instruments, were able to discriminate the presence of distress, as was found to be the case in another sample of the general population (Offidani and Ruini, 2012).

Primary care. The DCPR clinical interview for assessment of allostatic overload (Fava et al., 2017) was used in 200 patients in primary care (Piolanti et al., 2019). The PSI (Sonino and Fava, 1998; Piolanti et al., 2016), the CID (Paykel, 1985; Guidi et al., 2011) and the 12-Item Short-Form Health Survey (SF-12) (Ware et al., 1996) were administered. Thirty-one patients (15.5%) satisfied the clinimetric criteria for allostatic overload, which was the most frequently reported DCPR syndrome. Interestingly, of patients diagnosed with allostatic overload, 58% did not meet the criteria for any DSM-5 psychiatric disorder. (American Psychiatric Association, 2013). Subgroup comparisons revealed significantly higher levels of distress and lower scores of psychological well-being and quality of life among primary care patients presenting with allostatic overload compared to those without.

Cardiovascular disease. The criteria for allostatic overload were applied in several studies to patients with cardiovascular disease. In outpatients with essential hypertension and coronary heart disease (Porcelli et al., 2012), allostatic overload was found to be related to poorer psychosocial functioning, higher rates of psychopathology (mainly mood and anxiety disorders) and a higher disease-related emotional burden with associated abnormal illness behavior, somatization symptoms and irritability. Among patients with atrial fibrillation (Offidani et al., 2013), the presence of allostatic overload based on clinimetric criteria was found to be associated with increased psychological distress (e.g., depressive and anxiety disorders). In a study of outpatients with congestive heart failure (Guidi et al., 2016), 32.9% were classified as having allostatic overload. Significant differences were found with regard to gender, with women being more likely to report

allostatic overload than men. Overall, significantly higher levels of anxiety and depression, as reported either by self-rated Symptom Questionnaire (Kellner, 1987) or by observer-rated CID (Paykel, 1985; Guidi et al., 2011), were reported by patients with allostatic overload. Among cardiac risk factors, hyperglycemia was found to be significantly associated with the presence of allostatic overload. In patients with implantable cardioverter defibrillator (ICD) (Gostoli et al., 2016), the presence of allostatic overload before implantation was the only significant predictor, unlike other traditional psychological and cardiac risk factors, of subsequent negative cardiac outcomes, including post-ICD complications and death.

Fibromyalgia. A recent preliminary study (Leombruni et al., 2019) conducted on 104 female outpatients with fibromyalgia, evaluated the prevalence of psychosomatic syndromes by means of the DCPR criteria (Fava et al., 2017) and found allostatic overload in 25% of the sample. This was the second more frequent diagnosis after persistent somatization (51.6%).

Breast cancer. Allostatic overload has proven to be a sensitive parameter also in breast cancer. A study comparing 60 breast cancer survivors with 60 healthy controls, who reported major life events other than cancer, showed that allostatic overload was more common among cancer survivors (52%) than healthy controls (33%). Breast cancer survivors without allostatic overload presented greater posttraumatic growth compared to both survivors and controls with allostatic overload, especially in terms of personal strength and positive spiritual changes (Ruini et al., 2015). This is consistent with the view that recovery means not just going back to where one was before falling ill, but growing from the experience (Fava, 2016), in a life-course health development trajectory (Schmale, 1969; Halfon et al., 2014; Fava and Guidi, 2019).

6. Case illustrations

The clinical utility of the trans-diagnostic identification of allostatic overload can be best appreciated within a clinimetric approach. This adds to customary taxonomy incremental clinical information that

demarcates major prognostic and therapeutic differences (Fava et al., 2012, 2018). Macroanalysis is a clinimetric method that establishes relationships among co-occurring syndromes and clinical problems as well as therapeutic targets and their order of priority (Fava et al., 2012; Fava and Sonino, 2009; Sonino and Peruzzi, 2009).

Case 1. Mr. X is a 57-year-old man with essential hypertension displaying poor blood pressure control (despite treatment with ACE inhibitor and diuretic in combination). He is married, with a daughter in her early twenties,; he complains about difficulties both within the family (repeated frictions with his wife) and at work (an unexpected reduction in working hours leading to financial constraints). A specific psychiatric disorder according to DSM-5 criteria (American Psychiatric Association, 2013) was not detected, yet the clinimetric interview (Table 2) disclosed the presence of allostatic overload (he felt overwhelmed by problems and demands of everyday life), moderate symptoms of anxiety (feeling tense, irritable, difficulty falling asleep), as well as impairments in environmental mastery (he felt difficulties in managing everyday affairs and in exploring options when making decisions). Functional relationships among these different problem areas were established according to macro-analysis (Figure 2). The specialist (an internist and endocrinologist) treating the patient, alerted by the presence of allostatic overload, prescribed a benzodiazepine (clonazepam) at low doses for decreasing his state of arousal and improving sleep (Balon et al., 2018; Benasi et al., 2018). She also referred him to psychotherapy, which consisted of the sequential combination of Cognitive Behavior Therapy (CBT) and Well-Being Therapy (WBT) (Fava, 2016).

Both interventions were instrumental in inducing lifestyle changes that decreased the allostatic overload. After a few months, the patient regained control of his blood pressure and showed improvement in dimensions of psychological well-being.

Case 2. Ms. Y is a 42-year-old woman, divorced, with a 7-year-old child. She was diagnosed with major depressive disorder 1 year before, and was prescribed by a psychiatrist an antidepressant medication (fluoxetine), that she is still taking at the same dose (20 mg/day). Clinical interviewing revealed the

presence of residual depressive symptoms (lack of energy, loss of interest in things, sadness). Assessment with the clinimetric interview (Table 2) disclosed a state of allostatic overload (mostly related to legal problems with co-parenting and repeated troubles at work), low environmental mastery (difficulties in managing things of everyday life) and significant impairment in social functioning. By macroanalysis these clinical data were organized in a comprehensive framework for clinical reasoning (Figure 3). The assessment of allostatic overload alerted the psychiatrist to the risk for relapse (Paykel and Tanner, 1976) and suggested the usefulness of adding a psychotherapeutic approach to pharmacotherapy. CBT and WBT (Fava, 2016) reduced the allostatic load. Fluoxetine was successfully discontinued (Fava and Belaise, 2018) during psychotherapy. The patient is well and drug-free at a 2-year follow-up.

The two clinical cases illustrate how identification of allostatic overload may add crucial to medical and psychiatric diagnoses. The presence of biomarkers that are consistent with allostatic overload may reinforce the clinical data.

7. Conclusions

Biomarkers for allostatic load/overload express a state of the body systems, but do not provide information on the underlying individual experiential causes. The clinimetric criteria for allostatic overload fill this gap. They have yielded promising results in studies conducted both in the general population and in the setting of various medical conditions. The results should be interpreted with caution in view of their preliminary nature. Nonetheless, these clinimetric tools, merging different clinical information otherwise assessed by several instruments, were able to discriminate the presence of psychological distress.

There are a number of potential applications. In research, they may provide the missing link between clinical states and biomarkers. In clinical practice, they may guide the decision process by increasing the predictive power of the assessment procedure (Fava et al., 2012). Allostatic overload calls for close monitoring of the clinical situation (e.g., risk of relapse in a depressed patient, poor response to

treatment in a hypertensive subject). In case of functional medical disturbances, the presence of allostatic overload may contribute to explain symptom production and illness configuration (Fava and Sonino, 2009, 2017; Sonino and Peruzzi, 2009). Finally, the clinical characterization of allostatic overload may shed some light and offer some remedies to the post-hospital syndrome, a period of enhanced vulnerability to disease and to adverse events (Goldwater et al., 2018).

The identification of a state of allostatic overload may point to the use of psychotherapeutic strategies for improving coping with stress situations (Fava, 2016; Henningsen et al., 2018; Lindsater et al., 2018), and induce lifestyle modifications and pursuit of emotional well-being, whose importance is increasingly recognized in clinical medicine (Rippe, 2019) and psychiatry (Fava and Guidi, 2019).

Use of these clinimetric tools can increase the number of people screened, set the use of biomarkers in a clinical context, and broaden dissemination of measures to prevent or decrease the negative impact of toxic stress on health.

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Table 1. Clinical criteria for allostatic overload (A through B are required)

Criterion A	The presence of a current identifiable source of distress in the form of recent life events and/or chronic stress; the stressor is judged to tax or exceed the individual coping skills when its full nature and full circumstances are evaluated
Criterion B	The stressor is associated with one or more of the following features, which have occurred within 6 months after the onset of the stressor: 1. at least two of the following symptoms: difficulty falling asleep, restless sleep, early morning awakening, lack of energy, dizziness, generalized anxiety, irritability, sadness, demoralization 2. significant impairment in social or occupational functioning 3. significant impairment in environmental mastery (feeling overwhelmed by the demands of everyday life)

Table 2. Diagnostic interview for the determination of allostatic overload

ALLOSTATIC OVERLOAD			
Criteria		**Answer**	
Criterion A: The presence of at least one current identifiable source of distress in the form of recent life events and/or chronic stress; the stressor is judged to tax or exceed the individual coping skills when its full nature and full circumstances are evaluated	**A1.** In the last 12 months, ☐ Did a family member or a close friend die? ☐ Did you separate or divorce from your partner? ☐ Did you change job? ☐ Did you move? ☐ Did you have severe economic difficulties? ☐ Did you have legal problems? ☐ Did you start a new relationship? ☐ Did you feel under pressure at work? ☐ Did you have problems with co-workers? ☐ Have you been a victim of bullying, stalking or severe interpersonal pressure? ☐ Did you have problems with your spouse / partner or other family members? ☐ Did you feel tension at home? ☐ Has at least one family member been seriously ill? ☐ OTHER _____ _____ _____	YES	NO

	A2. Have you had the feeling that life is asking you too much?	YES	NO
Criterion B: The stressor is associated with one or more of the following features, which have occurred within 6 months after the onset of the stressor: (1) At least two of the following symptoms: difficulty falling asleep, restless sleep, early morning awakening, lack of energy, dizziness, generalized anxiety, irritability, sadness, demoralization	**B1.** Within 6 months after the onset of (NAME OF THE STRESSOR), ☐ Did it happen to take a long time to fall asleep? ☐ Did you wake up many times during the night? ☐ Did you wake up too early and could not get back to sleep? ☐ Did you feel tired, without energy? ☐ Did you feel a sense of instability, dizziness? ☐ Did you feel nervous or anxious? ☐ Did you feel irritable? ☐ Did you feel sad or depressed? ☐ Did you feel demoralized?	YES	NO
(2) Significant impairment in social or occupational functioning	**B2.** Did you have problems or difficulties at work, at home or in relationships with other people?	YES	NO
(3) Significant impairment in environmental mastery (feeling overwhelmed by the demands of everyday life)	**B3.** Did you feel overwhelmed by the demands of everyday life?	YES	NO

Diagnosis of ALLOSTATIC OVERLOAD

A1 = YES

+

A2 = YES

+

B1 and/or B2 and/or B3 = YES

□ YES **□ NO**

Figure 1. Mechanisms of allostatic overload

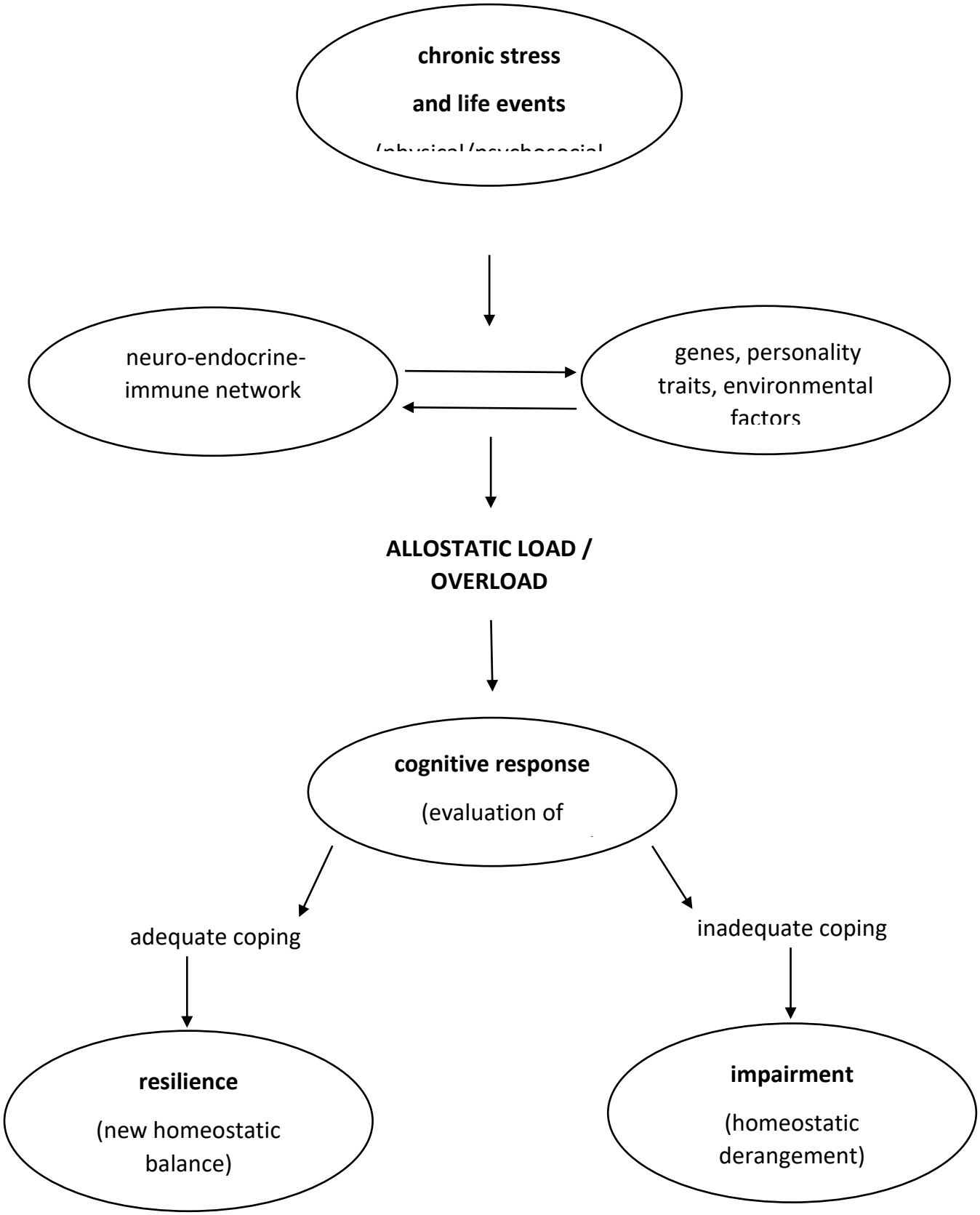

Figure 2. Assessment by macroanalysis of case 1 and therapeutic approaches

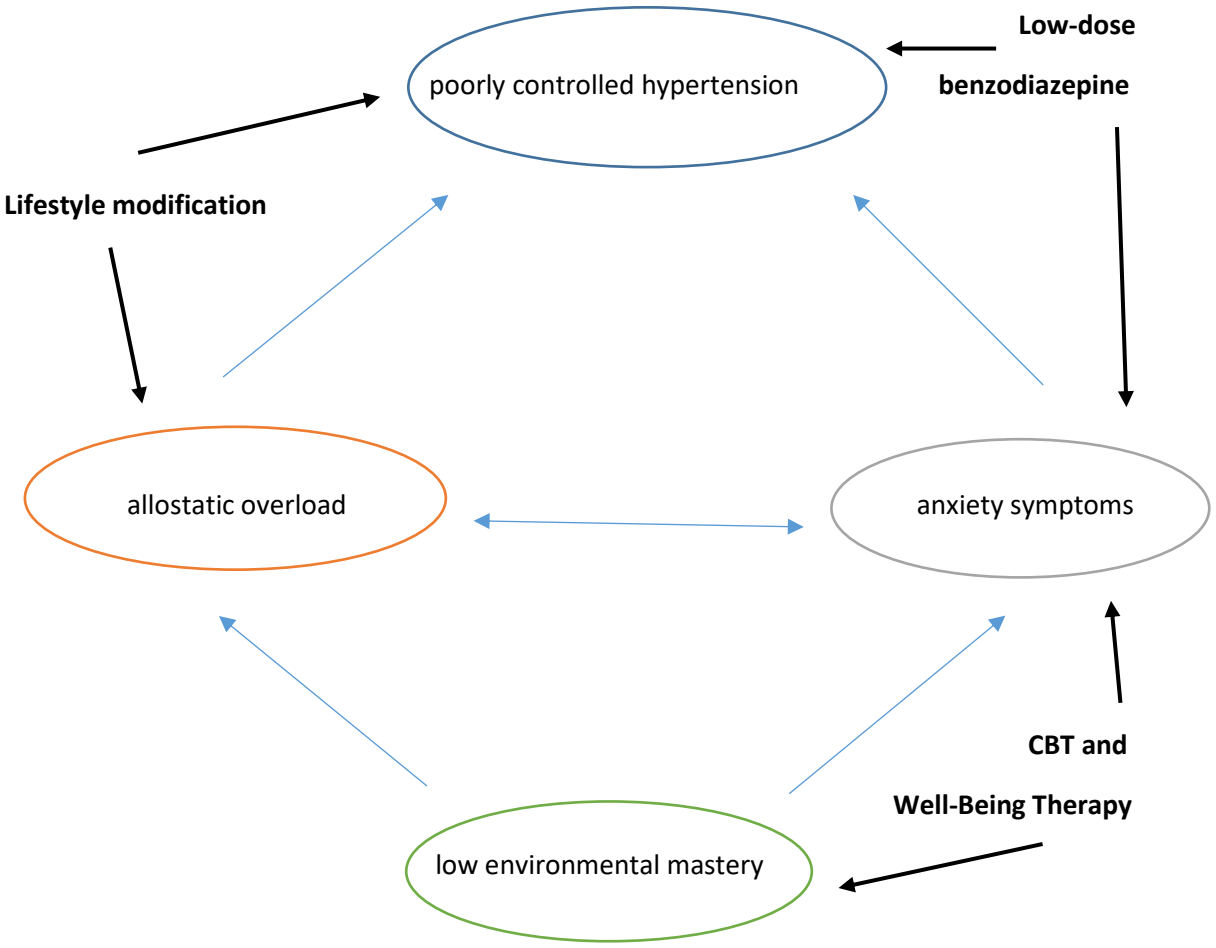

Figure 3. Assessment by macroanalysis of case 2 and therapeutic approaches