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Not one thing at a time: When concomitant multiple stressors produce a transdiagnostic clinical picture

Goldstein Ferber S *et al*. Multiplicity of concomitant stressors and mixed clinical picture

Abstract

A condition of exposure to multiple stressors resulting in a mixed clinical picture spanning conventional categories without meeting any of them in full, encompasses a risk for a list of comorbidities preventing appropriate prevention and treatment. New transformative transdiagnostic approaches suggest changes spanning conventional categories. They base their systems of classification on biomarkers as well as on brain structural and functional dysregulation as associated with behavioral and emotional symptoms. These new approaches received critiques for not being specific enough and for suggesting few biomarkers for psychopathology as a whole. Therefore, they risk the value of differential diagnosis for appropriate prevention and treatment. Multiplicity of stressors has been considered mostly during and following catastrophes, without considering the resulting mixed clinical picture and life event concomitant stressors. We herewith suggest a new category within the conventional classification systems: The complex stress reaction syndrome, for a condition of multiplicity of stressors, which showed a mixed clinical picture for daily life in the post coronavirus disease 2019 era, in the general population. We argue that this condition may be relevant to daily, regular life, across the lifespan, and beyond conditions of catastrophes. We further argue that this condition may worsen without professional care and it may develop into a severe mental health disorder, more costly to health systems and the suffering individuals. Means for derived prevention and treatment are discussed.

Key Words: Transdiagnostic; Multiple stressors; Clinical picture; Prevention; Treatment; Interpersonal psychotherapy; Cognitive behavioral therapy

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Core Tip: Multiplicity of stressors has been considered mostly during and following catastrophes, without considering the resulting mixed clinical picture and life event concomitant stressors. We herewith suggest a new category within the conventional classification systems: The complex stress reaction syndrome, for a condition of multiplicity of stressors, which showed a mixed clinical picture for daily life in the post coronavirus disease 2019 era, in the general population. We argue that this condition may be relevant to daily, regular life, across the lifespan, and beyond conditions of catastrophes.

INTRODUCTION

Many people with mental health complaints present a mixed clinical picture. Often none of the complaints meet the full criteria of any of the conventional classifications. Possibly, several categories are met (though not completely), leading to a list of comorbidities. This precludes clear diagnosis, prevention and treatment.

There are at least 4 different suggestions to revise classical classifications into transdiagnostic approaches: Hierarchical Taxonomy to Psychopathology[1], Research Domain Criteria[2], Bipolar-Schizophrenia Network on intermediate phenotypes[3,4], and Neuroscience-Based Nomenclature[5]. These suggested new classification systems are based on neuroanatomic findings that several brain areas show similar functionality and structure in various conventional categories[6-9]. However, others have commented on these data that they lack specificity, as the biomarkers show relevance over too many mental disorders[10]. Thus, many current conventional classification categories are gathered in the transformative systems into one pool of psychopathology, preventing consequent application of accurate prevention and treatment per each disorder including the missing clinical attention to individual differences.

Part of the mixed clinical pictures involves the concomitant experience of multiple stressors. As it arises from our literature search using PubMed, Google Scholar and *Reference Citation Analysis* (RCA), the impact of multiple stressors has been discussed by cutting edge papers mostly in the context of disasters such as hurricanes, floods, war

and in drastic conditions experienced by refugees and immigrants and in the coronavirus disease 2019 (COVID-19) era, with similarities between the impacts in these types of conditions across the lifespan, *e.g.*,[11-14]. The most common psychiatric outcomes reported are post-traumatic stress disorder (PTSD) and depression[15-20]. There are scarce reports on multiple stressors in daily life as related to the development of psychiatric disorders. Some of these reports relate to stressors in the workplace, economic hardships and the impact of urbanization[21-23]. Surprisingly, here also PTSD and depression are the common outcomes. The diagnosis of these two disorders in such different types of multiple stressors calls for attention and re-evaluation. Thus, the aim of the current commentary is to suggest a new potential category for the conventional diagnostic system, which will include conditions of mixed clinical pictures with more than one stressor identified.

As clinicians, we encountered a condition in which many patients showed mixed symptomatology, spanning conventional categories, without fully meeting all the conventional criteria of any of these categories during the multi-stressor COVID-19 outbreak. Our literature review supported our observations[24]. In a following empirical bi-national study, using representative, large samples[25], we further found that combinations of several mental health symptoms studied, PTSD, phobia, depression, anxiety and posttraumatic stress symptoms, were more prevalent than combinations with fewer symptoms, with no majorities-minorities differences in both Italy and Israel[25]. We termed this mixed clinical picture complex stress reaction syndrome (CSRS). CSRS includes type A (a psychiatric part) and type B (a neuropsychiatric part for the long-COVID component, excluding systemic symptoms)[24,25]. As more cross-cultural studies of the CSRS are warranted, we are currently conducting such an international study with participants from 8 diverse countries located in the Middle East, Europe, Australia and North America.

In this commentary we suggest that the CSRS type A (the psychiatric part, not including type B) may explain mixed clinical pictures in conditions of multiplicity of significant stressful life events in the post-COVID era. Thus, we argue that in the

general population, experiencing concomitant multiplicity of life events-related stressors may account for the development of a mixed type of mental health disorder, not only in conditions of catastrophes (see Figure 1).

Differential diagnosis

For differential diagnosis, the CSRS (type A) may be compared to: (1) Diagnosis of adjustment disorder rules out PTSD and bereavement, and it displays a short stressor onset-symptoms occurrence latency; (2) PTSD diagnosis includes exposure to one frightening stressor; (3) Obsessional thoughts are ego-syntonic by definition. The behaviors related to extrinsic stressors are clearly not included in the obsessive-compulsive disorder (OCD) conventional category; (4) Diagnosis of acute stress disorder implies a simpler stressor and a specific symptom response; (5) The criteria for defining generalized anxiety disorder list excessive worrying (on diverse issues) and shifting back and forth among them, thus not implying the multiplicity of stressors and a mixed clinical picture; (6) The diagnosis of major depression disorder includes anhedonia, low affect, psychomotor agitation, unfitting guilt feelings, diminished drive and energy, trouble concentrating, and indecisiveness with no other types of symptomatology which are included in a mixed clinical picture; and (7) C-PTSD is described as the result of a series of traumatic events, which is repetitive and hard to escape but does not include a mixed clinical picture beyond some PTSD conventional criteria. It also describes a series of events and not the simultaneous occurrence of multiple stressors as the possible etiological source for psychopathology.

Prevention

The impact of multiple concomitant stressors depends on individual subjective perception and stress reaction tendencies[26]. The immediate question is what can prevent the emergence of pathological stress reactions, spanning several conventional categories. In a previous study we found that close relationships may protect the individual across the types of psychopathology investigated, spanning anxiety,

depression, PTSD and OCD criteria, in conditions of multiple stressors[27]. The means for illness prevention and enhanced coping are therefore suggested as keeping close relationships active. Public and media educational programs for conditions of multiplicity of life stressful events with transdiagnostic potential consequences, aimed at enhancing individual resilience by utilization of social networks, are herewith suggested, evidence-based[27,28].

Treatment

We suggest a combined treatment approach of interpersonal psychotherapy (IPT) and cognitive behavioral therapy (CBT), two evidence-based and cost-effective methods, designed as short-term therapies and found to be equally effective to medications[29] in comparative studies[30,31]. Enhanced close relationships by techniques of problematic interpersonal relations analysis, resolution and role playing adapted from IPT[32], may increase emotional tolerance to accumulating stress emerging from concomitant origins. Our suggested combined psychotherapeutic approach also requires the blending of CBT separate protocols, including techniques for stress reduction and correction of cognitive distortions, rather than following one protocol separately or as recently suggested, one mandatory unified protocol for all types of symptomology[33-36].

We suggested previously that when exposed to multiplicity of stressors, the lack of clear goals implies the diffusion of actions[37]. This could be a risk factor for effective treatment of patients confronted with this type of condensed stressful experience. To overcome this risk and also to respect individual differences, a patient-specific and session-specific therapeutic strategy of assigning clear goals for adaptive coping is warranted, rather than working through a reparation condition or just attempting to eliminate the identified external stressors.

DISCUSSION

The origins of CSRS

CSRS emerged from the robust transdiagnostic clinical picture during and following the pandemic[38]. The World Health Organization indicates a prevalence of 22% of a mixed picture including depression, anxiety, PTSD, and general distress, fatigue, irritability and anger in the general population following the experience of war or natural disaster[39]. Transdiagnostic approaches to classifications were proposed even prior to the COVID-19 pandemic[1-4]. Here we argue that the impact of multiple stressors in daily life is a neglected issue in traditional classifications.

What was probably different about the COVID-19 pandemic compared to previous catastrophes was its global scale and the fact that it was covered extensively by the social, electronic, and print media. This factor may be regarded as an additional stressor in daily life beyond disasters. Whether media use is a source of social support, especially for young people[27,40,41] or a daily life stressor in the form of bombardment of information[42], is still a topic under scientific debate and probably age-related with large inter-individual variance.

Although there is enough evidence to suggest that the mental health of the population deteriorated following the pandemic[43], there is some suggestion that the extent of deterioration was less than anticipated[44,45]. In any case, epidemiological studies have shown that anxiety, depression, functional somatic, and even obsessional symptoms can coexist at the population or the community level[38,46,47], supporting our transdiagnostic views and the CSRS.

Inclusion of long COVID symptoms in the CSRS may create the same psychological *vs* physical dispute that we have witnessed with chronic fatigue syndrome or myalgic encephalomyelitis, but we include in the CSRS just neuropsychiatric symptoms, while systemic components of long COVID are excluded. In support of our view, studies that have already started appearing suggest that the long COVID syndrome is more likely to be associated with psychosocial factors rather than the COVID infection itself[48].

Thus, the origins of CSRS are rooted in the multi-faceted stress of the pandemic and its impact on mental health including its residuals in the post COVID era. The relevance of concomitant stressors included in daily life, under regular, non-catastrophic

conditions, and their association with a mixed clinical picture, is gradually becoming apparent.

The CSRS within the debate on psychiatric nosology

Our opinion goes beyond conventional approaches for construction of psychiatric taxonomy. Alternative concepts of psychiatric validity include controversies between validation of nosological structures (typical for medicine) as compared to prototype, cluster and dimensional diagnosis of mental disorders[49]. While the field of psychiatry moved towards more medically oriented nomothetic knowledge, alternative groups which we follow in our empirical and review papers, suggest that the field has to move away from this type of knowledge towards a more ideographic and subjective approach to psychopathology[49].

The main differences between the validity of dimensional diagnostics and that of traditional nosology are apparent in several aspects: (1) In traditional approaches, mental pathology is regarded as a strict drift from acceptable norms while the transdiagnostic views, similar to ours, suggest an axis between normal and psychopathological conditions; (2) In dimensional approaches co-existing psychopathological states appear in parallel along with personal strengths and capacities for resilience, unlike traditional nomenclature; (3) Dimensional approaches to the convergent and divergent validity of a cluster or co-existence of different pathologies without meeting a full criteria of any category in the conventional systems, such as the CSRS, do justice to the patient and the entire individual clinical picture he or she describes to the clinician, while traditional approaches prefer multiple comorbidities; and (4) The dimensional approaches such as the CSRS, unlike convention systems, emphasize subjective complaints of the patient (symptoms) rather than signs judged by the clinician. By that, these dimensional approaches are shifting the focus from the powerful societies of professionals towards the patient's subjectivity, and they recognize that professionals too, have their own subjective perspectives to consider before endorsing a diagnosis based only on signs.

Specifically, the CSRS has shown high reliability, as in two different countries and with two different methodologies the same results were found[25]. Additionally, the CSRS has shown high convergent and divergent validity as a combination of several identified stress symptoms, without meeting any full conventional category. These findings suggest a complex and unique type of reactivity to multiplicity of stressors. Other combinations suggested earlier, as complex anxiety and depression[50] or complex post traumatic stress disorder, showed validity for inclusion of just two conventional categories[51] while others showed a too wide range of inclusion, ruling out the potential judgement of divergent validly[10].

We acknowledge the importance of biological validation of psychiatric illness, but this still cannot be utilized for a treatment per any specified condition until the field of neuropsychiatric science advances considerably. The CSRS implies symptoms more than signs and subjectivity more than objectivity. The treatment derived from the CSRS would be patient-specific and session-specific, as human experience may go back and forth on the axis of elevated symptomology *vs* resilience and coping. Therefore, the notion of session-specific treatment requires the clinician's diagnostic effort at every given session to reevaluate the patient's symptomology for progression *vs* regression and to offer treatment accordingly. We propose that the human experience transits along time that elapses and a condition may be judged for a given patient, in a given environment at a given moment, considering how the observed syndrome has been individually experience-shaped[52-55].

It was noted earlier that the empirical validation used as the basis of conventional categories has been mostly regression statistical analyses with a weak basis for causality[49]. Contrary to any etiological arguments, we argue that the CSRS represents an association between multiplicity of stressors and a mixed clinical picture, which is worth to treat to avoid further increase in the patient's stress reactivity and future limitations of his or her resilience capacities.

We locate CSRS within the blend of the biopsychosocial model (BPS)[56] and the person-centered medicine (PCM) approach[57], as the novel CSRS is related to exogenic

stressors (BPS) and occurs as a subjective complex stress reaction of the patient (PCM). Thus, as outlined here and according to our binational research design and findings[25], the CSRS falls within the post-modern dimensional approaches more than within any strict nosology, for better prevention and treatment. CSRS was designed and investigated from a humanistic perspective, arguing that mental health is not represented by the lack of psychopathology, while psychopathology, in turn, is a condition with an indication to treat and may be reversible.

CONCLUSION

Transdiagnostic considerations towards a change in the classification of mental disorders can be accomplished within the existing systems without ruling out the importance of differential diagnosis if these conventional systems will start to include transdiagnostic phenomena as legitimate conditions for treatment and care. This reduces the risk of diagnosing too many comorbidities and by that precluding appropriate prevention and treatment. We argue that the syndrome termed as CSRS better identifies those patients reacting in a manner that spans several conventional diagnostic categories following exposure to concomitant multiple stressors. Unlike approaches that argue for complete transformation of conventional classifications[1-5], we claim that that a specific diagnosis concerning multiplicity of stressors that result in a mixed clinical picture, is a potential contribution to revised Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases for more accurate derived prevention and treatment. The future will tell if the openness to include post-modern transdiagnostic approaches to accurately serve more patients in need and to facilitate clinical practice of each individual psychiatrist, will be part of the discussions on the next revisions of the Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases or that the debate and crisis in psychiatry[58] will continue.

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