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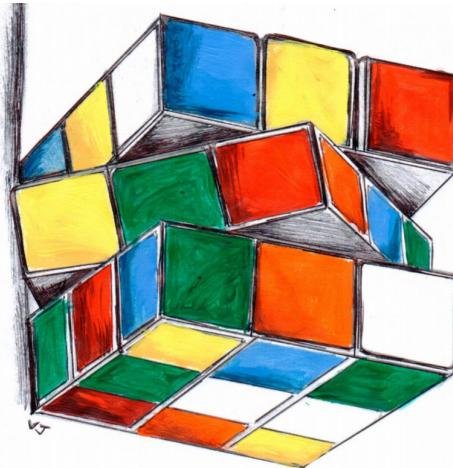
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# **STRESS AND STRUGGLES**

**THE COMPREHENSIVE BOOK OF  
STRESS, MENTAL HEALTH &  
MENTAL ILLNESS**



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# **STRESS AND STRUGGLES**

## **THE COMPREHENSIVE BOOK ON STRESS, MENTAL HEALTH AND MENTAL ILLNESS**

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## **FOREWORD**

Professionals have always been discussing the topic of stress and its impact on well-being. Stress is a common experience, and most people manage without experiencing serious health problems. However, if stress is overwhelming or chronic it can affect both physical and mental health. Stress is a complex subject due to varied meaning, lack of uniform application of stress concepts such as definition and measurement. The association of stress and mental illness is well known, and psychiatric literature provides information about different dimensions of stress.

This book is a notable addition to the literature on this topic. This book consists of multiple chapters covering several aspects of stress including biological, psychological, and social issues with a focus on specific stress related disorders, relations of stress to different psychiatric disorders and general management principles. Altogether, this book gives an excellent overview of the topic. Different chapters are highly relevant to the changing global landscape and current perspectives and can be useful for its relevance to many disciplines.

The authors bring together the basics of stress, and its effect on mental disorders and on special population as well as management of stress at different levels. The contributing authors are experienced professionals working in the field of mental health from several specialities in mental health. They are having either special interest in stress and stress related disorders or are involved in teaching and training programmes on this issue. It is relevant for all health professionals in general and for mental health professionals in specific because of its relevance to mental health.

Although the primary targets of the book may be higher trainees and postgraduate students in psychiatry and allied mental health specialities, it is expected that professionals from other disciplines, including clinical psychology, social work and psychiatric nursing will also find this book highly valuable. This is also a useful book for practicing psychiatrists and specialists of other medical disciplines. The other important groups who would benefit may include researchers, academicians, and health policies planners.

Editors of this book, Bettahalasoor Somashekhar, Narayana Manjunatha and Santosh Kumar Chaturvedi are well acclaimed and much-admired clinicians, researchers and teachers and I would wish that this book will have a significant national, regional & international audience.

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## PREFACE

This book is a response to curiosity of trainees and medical students. The current generation of trainees are inquisitive, articulate and expect precise answers. Stress is one among the several topics on which they are seeking clarity. This is understandable as the literature on the stress is unclear, ambiguous and filled with individualistic views. The common resources trainees and medical students approach usually make an oblique reference to stress and switch to describing either causes or management of stress without addressing the fundamental issue about what stress is. In addition, the literature links stressors as aetiology of mental illnesses without definitive evidence leading to confusion about management of mental illness such as rationale for treatment of mental illness with drugs.

The following are some common questions professionals and trainees are looking for answers

*What is stress?*

*How is it assessed and measured?*

*Does stress cause mental illnesses?*

*Can people develop mental illness without stress or stressors?*

*Can stress be managed and prevented?*

And so on

It is challenging to answer the above questions precisely because most literature makes a reference on stress for almost all psychiatric disorders in a general sense without rationale or evidence to answer genuine doubts. Despite claims of stress being important, we did not find clinically agreed approach to understand its relationship with mental illness. In addition, there is no single source where all aspects of stress in relation to mental illness are available. We compiled a brief summary on stress and its relation to mental illness for teaching purposes and approached colleagues interested in teaching and research to help us out. The request was responded with such a spirit that the initial intention to make

a brief overview has turned into a comprehensive textbook containing more than 600 pages. More than 80 colleagues involved in teaching, research and interested in stress across the world have contributed to bring together several aspects of stress in one book. The content of each chapter is a distilled product of authors analysis on a specific aspect of stress from a sea of literature. Although the content of each chapter is comprehensive on its own, our primary aim to provide coherent understating of stress and its relationship to mental disorders has been retained. We did not intend to provide exhaustive review of literature however the content of each chapter provides valuable information and current trends.

The research on stress and mental illness has centred around the life events and expressed emotions. Psychological understanding of and research on stress has largely been limited to ‘fight and flight’ response. People under stress respond in many ways than just fight or flight, they may choose to ignore, deny, freeze, and see as an opportunity. Studying on the different response would provide better understanding effects of stress on person life, give new insights to their coping abilities and provide basis to explore avenues in the management of stress.

The book is organised by arbitrarily dividing the content into 5 parts covering specific aspects of stress and its relation to mental illnesses for practical reasons. However, they are not mutually exclusive, and a degree of overlap cannot be avoided.

Part I of the book provides basics of stress such as evolution of the concept of stress, meaning and definition, classification, biological and psychological aspect of stress. Part II to focus on the illnesses caused by stress such as trauma and stress related disorders (DSM-5) and disorders associated with stress (ICD 11). The focus of Part III of the book is on the relationship between stress and individual psychiatric disorders. Part IV focuses on the stress and specific populations. Finally, Part V of the book covers broad strategies on management of stress.

The book can be used several ways. Firstly, reader can have a comprehensive understanding of stress and its relation to mental disorders by reading through all parts. Secondly, each part of the book covers specific aspect of stress and the reader may choose a part of the book in which they are interested. Thirdly, wide range of topics on stress and its relation to mental disorders are covered and hence the book

can be used as a reference on a topic of choice by glancing the contents. Finally, although reader can choose any chapter, we would recommend medical students and postgraduate trainees to read part one to begin with as this section provides basics on stress and acts as foundation to grasp broader aspects of stress.

We hope that the book is helpful for postgraduate trainees in psychiatry, medicine, clinical psychology, social work and psychiatric nursing on several aspects of stress and its relation to mental illnesses. The book is also useful for psychiatrist and medical disciplines that come across patients with stress related disorders. In addition, researchers, academicians and policy makers who are interested in stress and related disorders would find the book useful.

*Bettahalasoor Somashekar*

*Narayana Manjunatha*

*Santosh K Chaturvedi*



## **Acknowledgements**

It has been a long journey from the conception of the idea of book 5 years ago to this final product. The lessons learnt in the process of achieving the feat was the importance of teamwork, convergence of intention and action, enthusiasm and persistence. Mere intention without action and teamwork results in distress. Teamwork with enthusiasm and common goal makes the stress positive, and fulfilling.

Several people directly and indirectly have contributed to accomplish the task. First and foremost, we are deeply grateful to all the authors for their exemplary contributions. The authors have spent time and energy outside of their routine work to write the chapters only on our request.

We would like to thank Dr Afzal Javed, President, World Psychiatric Association, for his constant encouragement, and for writing the Foreword.

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We would like to thank Dr Supriya Dastidar, Higher Specialist Trainee in Psychiatry for the poem and her son Anurag Dastidar for his drawings.

We thank Dr Yamini D for contributing few of her sketches to this book that has helped us to enhance the aesthetics further.

We would like to thank Aditi Printers for designing, formatting and printing the book.

Finally, we would like to thank our medical students and postgraduate trainees for stimulating and keeping us interested in the topic of stress and teaching.

We would like to thank profusely, the artists who created the cover design and the pictures the book.

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# Part I

## BASICS OF STRESS



*Part I of the book focuses on the basics of stress and sets opening remarks with an introduction, evolution of various conceptual issues of stress research, different explanatory models and classifications of stress, various biological effects of stress on the human being, theoretical models of stress and coping skills, as well as biological aspects of stress and its biomarkers including resilience. At the end of part I, the readers will understand various concepts of stress, its evolution, biological effects of stress, biomarkers of stress, and theoretical models of stress and coping skills.*

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# **AN INTRODUCTION TO STRESS AND MENTAL HEALTH**

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**OUTLINE**

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| <b>1. STRESS AND SOCIETY</b>            | <b>2. STRESS, HEALTH AND ILLNESS</b> |
| <b>3. STRESS AND MEDICAL CONDITIONS</b> | <b>4. CONCLUSIONS</b>                |

Stress is universal and not just a human experience. It happens in humans, animals, organisms without a nervous system, plants and even in inanimate objects such as metals (Huey et al., 2002; Romero et al., 2015). Stress in inanimate objects such as metal is conceptualised as resistance offered by the object to the external force. When external forces either compress (Push) or expand causing tension (Pull), the metal reacts by distorting itself to counterbalancing the forces. The force is called stress and the reaction of the metal is called strain. There are established formulas to quantify the force and reaction(strain) (Ionnides & Vosniadou, 2002). Similarly, in agriculture plants are considered to under stress if they are subjected to less than ideal conditions for growth and there are established methods of quantifying stress (Pandey et al., 2017).

However, stress in living organisms is more complex. In simplest terms, the common denominator of stress in living organisms seems to be simple activation of a survival process involving physiological arousal response to threatening or unpleasant stimuli. The manifestation of stress become increasingly complex as the

lifeform evolves into species with higher specialised functions. In organism with well-developed nervous systems the response to a stressor (threat) is both physical and emotional directed at survival. In humans with highly specialised complex organ systems the stress response is dynamic and multidimensional involving various faculties of human biological systems such as neuronal, hormonal and immune systems (Martin et al., 2011).

The study of stress is important for various reasons. “Stress” has been dubbed the “Health Epidemic of the 21st Century” by the World Health Organization (Fink, 2017). There is growing interest in stress among lay public, social scientist and medical professionals. The use of word stress in modern life especially of urban life is very common. There is a popular perception that stress is ubiquitous in modern life (Shields & Slavich, 2017). The discourse of stress in media influence common understanding and lay conception about stress. People associate a variety of subjective experience to stress, from a notion that it predisposes to illness to use stress as euphemism to express life challenges and daily life hassles. There is a popular belief that stress is on the increase in modern society due to people inability to keep up with the changing world in the form of fast pace of life, time pressure, working practices, an advancement in technologies (Yates., 2011; Lederbogen et al., 2011). The COVID pandemic, lockdowns and restrictions, and the new normal lifestyle have increased stress of living (Nair et al., 2020).

The notion that stress is bad for health seems to have been accepted unconditionally. It has been blamed for various illnesses from the common cold to cancer (Monroe & Slavich, 2016). In recent times stress has been attributed as a cause or contributor to almost all chronic non-communicable disease including mental illnesses (Salleh, 2008). Thus, literature on stress has been expanding both in the academic area and in the non-academic area in the form of self-help literature.

The definition of stress, health and illness are imprecise and subjective (Shields & Slavich, 2017). There are universally accepted definitions for Health and Illness however none for stress and the definition of stress has changed over time (Monroe & Slavich, 2016). The confusion about the definition of stress has contributed to difficulties in conducting a comprehensive research on the subject and to ascertain the role of it in health and illness. Although it is not possible to be certain whether stress causes illness unequivocally, there is enough evidence to suggest that stress has a role in health and illness.

## STRESS AND SOCIETY

The focus of this book is the role of stress in mental health and psychiatric disorders; however, brief reference is made regarding the relation of stress and society for the following reasons. Firstly, the societal factors shape the individual and secondly, stress does not happen in isolation.

The source of stress is both micro and macro environmental factors. The micro environmental factors include changes in the family structure, values, roles and increasing desire and expectation of self-reliance. The macro environment changes affecting population at large include political system, war, geographical conflicts, and environmental calamities. Social factors such as the increasing emphasis on socioeconomic status underpinned by dominant and subordinate roles and the expectation to conform to social norm are also macro environmental factors (Tominaga et al., 2007). Humans are both a victim and perpetrator of stress response. They seem to be the most common and severe stressor to oneself and others. Both animal and human studies on hierarchy have shown that being dominant in a community is self-protective but cause stress in others. Animal studies on baboon monkeys have shown that the leading cause of threat is another member of the species not the predator (Gesquiere et al., 2011).

## STRESS, HEALTH AND ILLNESS

There are contrasting theories of health and illness. The theories on illness have evolved over years starting with the germ theory, biomedical approach and to the current biopsychosocial model. The current understanding of health is that it is dynamic and multidimensional, a complex catalogue of factors interplay between the mind and body influenced by relationships, community, and so on. The body-mind dichotomy is not yet dead, but it is terminally ill.

The relationship between stress and health can be better understood by what Hans Hugo Bruno Selye, also known as the ‘father of stress’ (Fink, 2017; Tan & Yip, 2018) described as ‘biological suicide’ (Selye, 1976). He states that two kinds of pathogens direct and indirect pathogens cause illness. Direct pathogens (example bacteria, heat,) can harm the body physically while indirect pathogen, themselves do not cause the illness but damage the body by stimulating an inappropriate and

harmful fight against what is innocuous. He further stated that organisms respond by two kinds such as Syntoxic and Catotoxic responses. The *syntoxic* response is passive tolerance aimed at coping; the organism learns to live with the aggressor, in a kind of peaceful co-existence. *Catotoxic* is active process and it causes chemical change through production of destructive enzymes. In the course of evolution, living beings have learned to defend themselves against all kinds of assaults (both within body and in the environment) by these two mechanisms which help to put up with the aggressor (syntoxic) or destroy them (catotoxic) (Selye, 1973).

Disease can indirectly be caused by person's own inappropriate or excessive adaptive responses, for example, daily hassles may raise blood pressure. According to Selye, illness, and even death, can be a result of inappropriate responses to stressors. He asserted that fighting or even preparing to fight may result in increased sympathetic activity. He further elaborated that we do not always recognise what is and what is not worth fighting. He stated that from birth, to throughout life, the major problem for human being, is adaptation to maintain homeostasis (Selye, 1973)

Although exact mechanisms of how stress effect health are not known, various factors listed below indicate that there is a correlation between stress and illness (Schneiderman et al., 2005)

The likelihood that stress can cause illness raises many questions and opportunities in terms of interventions and preventative measures. The health care cost is escalating in last few decades for several reasons such as increase in life expectancy, change in the pattern of illness from infection to chronic non communicable illness and increased expectation from service users. However, there are only finite resources and therefore effective use of resource require appropriate prioritisation. It also helps economically for both individuals and society to plan health care (Altman et al., 2003).

Stress related intervention may therefore reduce the cost to the society if resources are invested in areas that cause or contribute to stress related illnesses. For example, changes in the pattern of illness over the last century clearly suggest that behaviour component is central to many of the new forms of illnesses. If more resources are spent on changing the behaviours that contribute to illness may in the long term have more positive effect on health and thereby reducing the cost

of health care. The benefits are both in decreasing the loss of productivity due to ill health and preventing stress related absences by providing health care to stress related illness.

Again the world is witnessing the re-emergence of infectious illness threatening the existence of human beings in year 2020 in the form of COVID-19 (Corona Virus Disease 2019) (Poon & Peiris, 2020). Covid-19 has caused significant distress across the countries, across different socio-economic strata and different professionals (Rehman et al., 2020) (Nanjundaswamy et al., 2020) (Chaturvedi, 2020). There are many guidelines came out to manage mental health and general health settings during this pandemic (Reddy & Jaisooriya, 2020). There are report of reverting back to behaviors related cultural heritage (Chaturvedi & Sharma, 2020). There are reports of neuropsychiatric aspects of COVID-19 reflection of stress besides biological effects of novel virus (Dinakaran et al., 2020).

## **STRESS AND MEDICAL CONDITIONS**

For the sake of simplicity in the textbook, authors classify medical conditions into physical and psychiatric disorders.

### **Stress and Physical Disorders**

Stress is believed to cause or influence the course of medical conditions such as Irritable bowel syndrome, hypertension, heart disease, diabetes and many other conditions (Cohen et al., 2007). It is also known to affect immunity with consequent increased susceptibility to infection and poor healing (McLeod, 2010). Although the focus of the book is on stress and mental disorders, a chapter has been dedicated on stress and physical disorders.

### **Stress, Mental Health, and Psychiatric (Mental) Disorder**

The study of stress and its relation to mental health is profitable for several reasons. *Firstly*, with a few exceptions, there is no aetiology identified for mental illness. Various attempts to explain psychiatric illness in terms of genetic, social, psychological or combination of the three has not yet been successful (Uher & Zwicker, 2017). Science has not yet provided a clear answer to the commonly held belief that psychiatric illnesses are triggered by something bad that has happened to person. *Secondly*, recent trend in mental health field shows increased medicalisation suffering due to social adversities, increased use of prescription drugs to deal with

mental health problems, and greater willingness to identify emotional suffering as mental illness that require professional help (Conrad & Sladden, 2013). *Thirdly*, there is plethora of psychosocial interventions particularly Cognitive Behaviour Therapy advocated for the treatment for various disorders. Although some of them are at least partially helpful, a careful cost-benefit analysis is required to ascertain their appropriate use (Dezetter et al., 2013) (Laynard et al., 2007). *Fourthly*, stress research helps to understand the impact of psychological, social and environmental factors on a person's mental health, onset of mental illness and role of preventative measures (Kessler et al., 2007). *Finally*, although the term stress was introduced into psychiatric literature long time ago, phenomenologically there is no agreement on what stress is; is it an emotion, thought, cognition or perception, or something else. Further focused studies on phenomenology of stress will help to understand the relation between stress and mental disorder that has been well known for several decades (Gallant, 1990). Stress can cause, precipitate a relapse and contribute in maintaining illnesses. There in an assumption that the onset of psychiatric disorders has been due to something that has happened in an individual's life, particularly adverse life circumstances (Sutin et al., 2010). It is a common observation of clinicians that the onset of several psychiatric illnesses coincides or precedes significant life events.

The causative role of adverse events is a difficult area to be certain about because adverse events are very common but not everyone develops mental health problems (Monroe & Slavich, 2016). It has been noted that an average, three significant unpleasant and distressing events happen to most people in a year. Therefore, it is quite natural for people to associate the onset of an illness to something unpleasant that has recently happened. It is usually the negative or unpleasant adversities that are associated with the onset of illness, particularly affective illness and it is rare to see onset of illness after success or positive life events. In the quest for finding aetiology for mental disorders, *stress* has been implicated as a cause. However, the exact role stress plays in mental disorder is not clear and it may not always be possible to be certain whether the stress (adverse event) is a *cause or consequence* of a mental illness. The association of stress and mental disorder may be coincidental. This is further complicated by fact that the age of onset of many psychiatric illnesses coincides with a period in people lives that is filled with many life changes and challenges. The available evidence suggests that adverse life events play a role in mental illness. However, the contribution of life events is small and at best seen as a triggering factor than as a cause.

The association of stress and mental disorders can be better understood by arbitrarily categorising them in the following four ways.

- *Coincidental*: Stress and mental disorders occur in a person independently without any relation to each other.
- *Stress cause mental disorders*: The aetiology of these mental disorders is presumed to be due to stress implying that they would not have occurred without stress. They include stress related disorders.
- *Stress contribute to mental disorders*: Stress act as predisposing, precipitating or maintaining factor for the mental illnesses.
- *Mental disorders cause Stress*: The manifestations and the consequences of mental illness cause stress.

**Stress and mental disorder exist coincidentally:** Stress and mental disorders may exist independently in a person without any relation to each other whatsoever. The meaning of stress among professionals and public is so broad and varied that anything can be associated with stress. Therefore, almost all mental disorders can be explained in terms of stress. This is especially true with public and professionals with limited knowledge and experience in dealing with mental health problems. In addition, the prevalence of stress is so high among the general population that almost everyone will have some stress at some time in their life and therefore it is not a surprise that the discourse regarding metal disorders centres on the stress.

**Stress causes mental disorders:** Stress related mental disorders are a group of disorders which are presumed to be caused by stress. In contemporary classification, two groups of illness are explained in relation to stress as aetiology. In the first group of disorders, presence of stress (usually described in terms of life events or trauma) is essential to make the diagnosis. In other words, the illness would not occur in the absence of stress. The presence of stress is not only necessary but also obvious in this group of disorders. They include acute stress disorder, post-traumatic stress disorder, adjustment disorder and reactive psychosis (acute and transient psychotic disorders with stress according to ICD -10). Acute stress or event stress is obvious in this group of disorders. In the second group of disorders, stress (psychosocial factors) may not be obvious at all the time but it is essential to make a diagnosis. In other words, stress is presumed to be the cause even it is not obvious or identified. They include the group of disorders which were traditionally known as neurotic disorders such as somatoform disorder, somatisation and

dissociative disorders (replace with ICD categories). while chronic stress is usually associated with somatisation and somatoform disorder, acute stress and episode stress is more often associated with dissociate disorders (Kienle et al., 2017; Reddy et al., 2019; Ginzburg & Solomon, 2011).

**Stress contributes to mental disorder:** All major mental illnesses can be correlated with significant life events. The degree of its association with onset of an illness is difficult to ascertain. Evidence indicates that there is excess of life events before the onset of major illnesses such as schizophrenia, bipolar disorder and depressive disorder. Evidence suggests that earlier episodes are triggered by the life events. This is accountable for only 20 percent of the cases suggesting that presence of stress is not necessary for the onset of illness (Ambelas, 1987). In this group of disorders stress does not cause but only precipitates illness in a person who otherwise would have developed the illness at some point of time in his life or he would have been protected from the illness if life event has not occurred.

**Mental disorders cause Stress:** The symptoms of mental illness occur in the context of relationship and affects everyone around them. Therefore, experiencing a mental health problem is not only stressful to the person suffering from the illness but also to the person who care them. Evidence suggests that people with mental illness have increased physical health mortality and morbidity. People with schizophrenia have 20% reduced life expectancy compared to normal population (Kilbourne et al., 2009). The most common cause of the mortality is cardiovascular illness which is associated with chronic stress (Manjunatha et al., 2019).

Thus, the inter relationship between stress and mental health is an intricate topic for discussion and provides scope for discussing numerous hypothesis about the causation of mental health problems. We hope that readers will enjoy reading each chapter about the role of stress in various mental illnesses in this book.

## CONCLUSIONS

Stress is ubiquitous; observed both in non-living and living. While the manifestation of stress in non-living things is a structural change or break of an object, the manifestation in living organisms is an attempt to survive and preserve. The dimension of stress has become complex with evolution, thus stress in human is dynamic and a complex interaction between environment and individual. Although the word stress is used with varied meaning, over the years understanding of

stress has widened. The work of Hans Selye has triggered research to explore the role stress in health and illness. In the last few decades, changes in the pattern of illnesses, increased longevity and advancement in medical sciences, non-communicable diseases including mental illness have become prominent. It is well known that behavioural component, a reflection of stress, plays an important role in most chronic medical and most psychosomatic conditions which can be mitigated by appropriate stress management. Although the role of stress in mental illness is well recognised, the approach to delineate it further is patchy. We hope that the clinical approach described in the chapter to understand the relation between stress and mental illness helps clinicians in their patient care and provides a basic framework to researchers for further exploration.

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## **CONCEPTUAL ISSUES OF STRESS**

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### **OUTLINE**

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| 1. INTRODUCTION  | 2. HISTORICAL ASPECTS: EVOLUTION OF THE STRESS CONCEPT |
| 3. DEFINITIONS   | 4. EXPLANATORY MODELS                                  |
| 5. CLASSIFICATION OF STRESS                                | 6. NEW TRENDS  |
| 7. THE SPECTRUM OF STRESS: FROM UNDERSTIMULATION TO TRAUMA | 8. CONCLUSIONS   |

## **INTRODUCTION**

Stress has been a lasting topic of interest for the general public, social scientists, medical professionals and political organisations. It is a buzz word used by the general public to describe many difficulties or challenges. The conceptual understanding of stress in the medical, social and psychological scientific communities varies widely by profession based on their theoretical orientation. There is no agreement on what stress means, let alone a universal definition.

Unfortunately, this has led to development of the stress as a concept being so broad that anything can be subsumed under and explained in terms of stress. The lack of clarity on the concept and definition of stress has therefore made it difficult to precisely measure for the purposes of understanding its impact on health, which in turn limits the full clinical utility of the stress concept.

Everyone knows and experiences ‘stress’ but commonly cannot easily explain it in words. Like happiness, success, and failure, stress is subjective and occurs in a context. It is not only subjective but also relative making it difficult to define in absolute terms. The term stress has been used by professionals and the lay public often with different meanings. The meaning is determined by several factors such as culture, individual characteristics such as personality and in professional use by research and experience. If we want to achieve a successful intervention to combat stress, then it is important that the meaning of it is the same to the public and professionals.

This chapter aims to address some of these issues through an overview of the concepts of stress from various dimensions.

## **HISTORICAL ASPECTS: EVOLUTION OF THE STRESS CONCEPT**

The concept of stress has changed over years both among public and professionals and is influenced by improvements and developments in several fields of medicine and social sciences. However, there is still no universally accepted understanding and the concept continues to be filled with confusion, controversy and inconsistencies.

A deeper understanding of the source of confusion will help in resolving controversies in the scientific community, misconceptions in popular media and the lay public about stress. It also avoids just adding new findings on stress from research based on false paradigms. In order to better understand the prevailing situation and future perspectives it is important to cover the background historical aspects and evolution of the stress concept. Reviewing the evolution also helps us in understanding of factors that have influenced the development of concepts and changes in the direction of stress discourse. These developing concepts also affect political, cultural and scientific aspects of stress research.

The evolution of stress concepts in relation to health can be understood by broadly categorising the developments into three periods:

1. Pre- Hans Selye period
2. Hans Selye and
3. Post- Hans Selye

### Pre- Hans Selye period

The concept of stress in humans' dates back to the 14th century and was used to refer to hardship, adversity or affliction. It continued to evolve over several hundred years with changing terminology. The concept of stress was first studied in engineering in the 17th century as a force applied to a material and the extent to which it could withstand the stress before breaking. This idea influenced models of stress in the subsequent centuries which viewed stress as a load or external force exerted on the social, psychological and physiological systems (Lazarus, 1999).

The notion of stress affecting health, particularly cardiovascular health has a long history. In 1628, William Harvey referred to the relation between mind and heart stating that activities that afflict mind in the form of pain or pleasure, fear or hope extend their influence on the heart. However, the importance of stress on health became widely recognised in the late 19<sup>th</sup> and early 20<sup>th</sup> century. The earliest studies on stress were based in physiology. In the second half of the 19th century, French physiologist Claude Bernard described that perfection of an organism depends on instant compensation of the internal environment (*Milieu intérieur* in French) to external variations. As such the goal of all vital mechanisms despite how varied they are is to maintain uniformity of the internal environment. This stability of the internal environment is the conditions for a free and independent life. (Gross, 1998). As such for organisms to survive independently they would need to adapt internally to what can be seen as external stressors.

Later work by Lewes in 1877 was supportive of Bernard's theory that organisms must preserve their integrity of internal structure which he called vital properties. However, he went on to postulate that these vital phenomena are inseparable to mental phenomena and that neural functions are integral elements to internal stability. This is supported by the work of Thomas Curling (1842) who identified gastric ulcers in response to severe burns. These are now viewed as part of stress-induced ulcers, caused in response to acute illness resulting in physiological change in the gastric mucosa. In 1867 Albert CT Billroth noted similar findings after major surgical intervention complicated by infections.

After half a century later American physiologist Walter B Cannon (1932) coined the term homeostasis to describe the concepts first eluded to by Bernard. He defined this as a steady state maintained by coordinated physiological processes. His earlier work in 1915 identified fight or flight responses which are changes in

the release of the hormone adrenaline in response to external or internal stimuli namely pain, fear, hunger and rage threatening homeostasis. These responses confer a survival advantage and form the basis of the evolutionary perspective of stress and he quotes “the quickness of the response measures the chances of survival in a struggle where the issue may be life or death”.

In this period there was a heavy focus on the physiological aspect of stress and the mind was considered by some to be a separate entity. However, Franz Alexander and his colleagues had become interested in relating personality characteristics within the framework of psychosomatic medicine to certain diseases. For example, he noted in his research ‘the frequency among peptic-ulcer patients of the hyper-active go go-getter type’ (Franz, 1950).

### **Hans Selye period**

Hans Selye was the first scientist to identify these adaptations in physiology in response to threats to homeostasis as “stress”.

Early in his medical career as a student, he noticed a generic nonspecific response from disease that threatens homeostasis. He observed that many patients though having differently diagnosed medical conditions showed a non-specific response to disease with several generic symptoms such as fatigue and loss of appetite (Seyle 1950; Tan & Yip 2018). He eventually in 1945 after years of extensive research coined the concept of the “general adaptation syndrome” to “integrate a number of seemingly quite unrelated observations into a single unified biologic system” (Selye, 1950). This concept was based on 3 stages: the alarm reaction, resistance and eventual exhaustion. Features of the first stage such as catabolism and haemoconcentration disappear during resistance and reappear in exhaustion. Once adaptation has occurred in resistance and providing energy is available theoretically, resistance could go on indefinitely. However eventually exhaustion sets in demonstrating that this adaptation process is finite, for example an animal can only cope with extreme cold up to a certain extent. The size of this is largely dependent on genetic factors. He explained this by comparison to a machine which gradually wears out even if the machine has enough fuel to function, and similarly man becomes a victim of constant wear and tear and will eventually give up with exhaustion. He stated that these stages are analogous to three stages of man. During childhood, man has low resistance and excessive responses to any kind of stimulus, during adulthood, he adapts to most things and

resistance increases for some and during senility irreversible loss of adaptability and eventual exhaustion ensues. (Selye, 1974).

Although he first used the word “stress” in an article co-authored with Thomas McKeown in 1935 ( Selye & McKeown 1935) to describe the adverse conditions female rats were subject to as part of experimentation it was not until his later works a decade later, that the term became more commonly used to describe the general adaptation syndrome. (Selye, 1946; Selye, 1950). Many other prominent people like Freud and Pavlov worked on issues related to stress during the contemporary period; however, it was the introduction of the general adaptation syndrome by Hans Selye that made a profound impact.

Over the years, the stress-related research expanded with the involvement of professionals from medicine, psychology, and sociology resulting in development of new concepts and explanations (e.g., effect of physical environment on occupation, coping, effect of war on soldiers, public, etc.)

Both Cannon’s theory and Selye’s theory focused on the physiological aspect of stress but not on the psychological aspect except that psychological stimuli can be possible stressors. As such though these two theories influenced stress research and formed the basis of neuroendocrine research into stress, but they did not clarify the process of psychological or social aspects of stress.

Harold Wolff (1953) a physician in his book on stress and disease floated the idea that life stress played a role in aetiology of disease, correlating physiological change with psychological aspects in several diseases. He viewed disease as an adaptive response to both physical and psychosocial stressors. Wolff’s examples of the development of reversible palsy in a soldier called to battle and the development of pain in a woman which eliminates the possibility of sexual intercourse with an unacceptable partner illustrate this. The notion that physical disease can manifest as a result of psychosocial stressors relates to the concept of psychosomatic medicine which was also developing to further explain how illness affects the person as a whole. The concepts were largely based in psychoanalysis in that there was some underlying emotional conflict manifesting as physical symptoms. In the following decade animal experiments demonstrated there was a behavioural component to psychosomatic illness and these theories became popularised. Miller (1969) through animal experimentation demonstrated that visceral responses in

rats could be learned based on rewards. He speculates that this could be a cause of psychosomatic symptoms and gives the example of a child who experiences a variety of autonomic symptoms such as pallor and faintness at the fear of going to school, who is then rewarded by his mother who keeps him off school, which then reinforces the cardiovascular system to produce these responses. Wolff simplifies this as when humans are rewarded by excessive solicitude whenever they complain of psychogenic visceral symptoms, they learn to develop the symptoms repeatedly until it becomes an established pattern of behaviour.

In 1945, the second world war provided another impetus to stress research with development of concepts such as combat stress. The interest in combat stress further expanded research on individual variability and vulnerability to stress (Grinker, 1945).

The developments in several scientific disciplines during this period helped further expand research on stress. For example, biochemistry helped in extraction and reliable and objective measurement of stress hormones such as adrenaline and cortisol. Similarly, the developments in psychophysiological technology allowed for precise measurement of variables such as heart rate, galvanic skin response and other indices of autonomic arousal.

Stress research from the 1950s expanded from military work into other areas to study on the effect of physical environments on performance, such as the impact on noise on performance of vigilance tasks (Broadbent, 1952) and researchers also became interested in the concepts of occupational stress (Smith 1955; Shepard 1954).

### **Post- Selye period**

The question remained however as to why people respond differently to stress with it resulting in disease in some but not others. The initial focus on physiological responses moved toward studying individual differences to stressful situations. From 1960 psychological research attempted to provide a theoretical account to explain individual differences to stress. In 1966 Richard Lazarus studied performance under stress and developed the concept of cognitive appraisal to explain these individual differences stating that stress is stressful if it is appraised that way by the individual. This not only helped in explaining individual differences but also helped in development of coping strategies.

In the same period sociological research was developing, looking at life events both positive and negative on health. A significant starting point in life events research was the development of the Social Readjustment Rating Scale (SRRS) by Holmes and Rahe (1967) to measure the stressfulness of the life events. With the beginning of life events research, the role of stress became more central to understanding illness. It paved the way to study environmental adversities on health and several studies showed that negative or stressful life events have negative effects on health (Salleh, 2008). Evidence also suggests that stress plays an important role in the onset, progress, treatment response and prognosis of several mental illnesses. They are dealt in depth in Part II of the book.

Also examined was the effect of social events such as riots on health, rates of suicide and mental illness in relation to social adversity which paved the way for development of a new concept of social support. Although there is conflicting evidence to support this idea, the evidence suggests that social support in the form of emotional support, instrumental help such as material and practical support reduce the negative effects of stress on health (Ozbay et al. 2008).

Life events research was criticised for various reasons, the most important of them are two. First, it fails to take into the account of individual variability in response to stress events by different people. Secondly, life events are complicated by socioeconomic factors therefore there are limitations to predicting the effect of life events in isolation on health. These criticisms have led to focus on individual factors and identification of variable demographic factors such as age, sex, employment status, social class, urbanisation as vulnerability factors.

This criticism has also led to more research in individual psychological factors. For example the identification of a Type A behaviour pattern by Rosenman et al., (1976) features of which such as aggression make a person prone to stress, which in turn was strongly related to the incidence of coronary disease.

In addition various psychological concepts such as the concept of hardiness (Kobasa 1979) self-efficacy theory (Bandura & Adams 1977) and locus of control (Rotter 1966) were developed.

The rise of cognitivism in 1970 influenced stress research with the development of cognitive theories and latter development of cognitive therapies.

Though research by Roseman et al., identified the type A behaviour pattern, it was cognitivism that was able to understand the underlying cognitive distortions or pathological cognitions which contribute to the development of type A behaviour pattern and the associated predisposition to stress and limitations of coping with it, thereby paving a role for cognitive therapies in managing stress responses as seen in such personality types.

Various cognitive models such as stress inoculation training (Meichenbaum 1977), attribution theory (Hilton & Slugoski 1986), and social comparison theory (Festinger 1954; Taylor et al. 1990) were put forward to explain and manage stress.

More recent research has looked at the stress beliefs and takes the view that those who perceive stress as good such as it provides an environment for motivation and to thrive find it will have less or even a positive impact on health than those who view it negatively. The former having better coping mechanisms for dealing with stress (Selye 1975; Lazarus 1993).

In summary, the concept of stress has developed over several years. Different views were held based on the prevailing popularity of the theory at that time. The understanding of stress further progressed with advances in natural sciences.

### Box 1. Key Points: Historical aspects: evolution of the stress concept

- The concept of stress continues to evolve, and inconsistencies remain.
- Origins of stress in humans are noted as early as the 14th century
- Scientific research into stress became popular from the early 20th century, with initially a largely physiological approach taken by Walter Cannon and Hans Selye.
- The role of psychological components to the stress concept developed from the 1960s with Richard Lazarus being a prominent pioneer in this field.
- Personality, life events and environmental conditions are all considered to be important factors in understanding the stress concept.

The concept of stress and the notion that it can influence health has been around for a long-time dating back to 1628 and there is a magnitude of literature on the topic. The advent of significant advances in the field began with Hans Selye's work on stress and the general adaptation syndrome, which not only popularised the concept of stress but also initiated an era of research and theoretical developments in medical branches and later in social sciences. Although the notion that life

events have a role in the onset of illness particularly psychosomatic illness has been recognised for many years, it is only in the last 50 years this notion has gained more acceptance in the scientific community.

## DEFINITIONS

Several terms such as stress, strain, stressor and stress response are used in stress literature. They are often used with varied meaning and interchangeably causing confusion. However, a definition is still necessary for communication, measurement and to study further. In the following section an attempt is made to provide clarity on these terms.

The term stress has been used loosely to describe several things, but it is often described in the context of what caused it or the consequence of it as opposed to the concept in itself. In other words what stress ‘does’ rather than what stress ‘is’. For non-professionals, stress refers to any difficulty which is out of their normal repertoire. On the other hand, professionals tend to focus on the quality and quantity of the issues before considering them as stress and centre on certain situations with specified factors. In daily language the term stress is commonly used to describe a negative emotional state, difficult situations, emphasise something or simply to describe mental health problems. If someone is talking about stress, they are often referring to one of the following

1. An event, circumstance or an issue which is demanding a need for change or call for action by an individual.
2. Explanation of the feeling, thinking or behaviour associated with a need for change when faced with a demand. The demand may be physical, emotional, psychological or social.

*Some of the definitions of stress are as follows*

According to the Oxford English Dictionary, stress is a) pressure or tension exerted on a material object, b) a state of mental or emotional strain or tension resulting from adverse or demanding circumstances c) physiological disturbance or damage caused to an organism by adverse circumstances d) particular emphasis or importance.

The National Health Service in Scotland, UK describes stress as the feeling of

being under too much mental or emotional pressure and that this turns into stress when feeling unable to cope.

The National Institute of Mental Health defines stress as the brain and body's response to any demand. The demand (change) may be positive, negative, real or perceived. The demand may be short lived, recurring or long term.

It is clear from the literature that stress is not a single entity. It is a combination of three components: the individual, environment and interaction between them. Accordingly, the definitions can be grouped into three categories or models namely the Physiological model, theories initially derived by Walter Canon and Hans Selye, the Engineering model, and the Psychological model. They are also respectively referred to as response based definition stimulus-based definitions, and interactional definitions.

#### Box 2. Key Points: Definitions

- Despite the confusion surrounding the meaning of stress definitions have been proposed to the public by health institutions and the Oxford English dictionary.
- A central theme in these definitions involve a demand placed on a person and the ensuing psychological and physiological response to this.

## EXPLANATORY MODELS

The definition of stress concepts can be grouped into three categories:

1. Response based definitions (Physiological approach) – conceptualise stress as a response to demand put on a subject and view that stress *happens in* man.
2. Stimulus based definitions (Engineering approach) – conceptualise stress as external events or circumstances and view that stress *happens to* man.
3. Interactional definitions (Psychological approach) – conceptualise stress as a product of the interaction between the environment and the individual. This model is further subdivided into the interactional model and transactional model.

All three groups of definitions encompass individual, environmental and interactional factors but with specific emphasis on one aspect. Thus, stress is

defined as a stimulus by the engineering model with a focus on the environment, as a response in the physiological approach focusing on the individual and as an interaction between the environment and the individual in the psychological model. These are briefly examined below.

### **Response based definition of stress (Physiological approach)**

These definitions conceptualise stress a physiological response to demand put on a subject. In other words, Stress *happens in* man. This model was proposed by Cannon in his fight and flight response theory (1915) and developed further by Hans Selye. In his 1946 paper, Selye described stress as a factor acting outside the organism such as anoxia, cold or muscular exercise and studied the physiological responses this produced. In his later work in 1950 he referred to this stimulus as a ‘stressor’ and the ensuing physiological reactions as the General Adaptation Syndrome or stress. The use of the word general to illustrate that the basic reaction pattern is always the same regardless of the stressor and it involves the autonomic and endocrine systems. He explained that this is a useful and normal physiological reaction and derailment of this process can result in disease, this does not happen in all or to the same degree hence some will develop disease and others not. He later addressed the controversy about the definition of stress stating that the confusion between stress as both an agent and a result can be avoided by the distinction between “stress” and “stressor”.

Although this model is popular and simple, it has been criticised for various reasons. First, defining stress merely in terms of physiological response is over simplistic and it cannot account for complexities of the stress process. For example, the fact that we exhibit physiological stress responses during periods of excitement and pleasure is not consistent with the idea of stress as a cause of ill health. In this regard, to overcome this Hans Selye introduced the terms eustress and distress to account for positive and negative effects of the stress response, ‘eustress’ being positive and enhances health and ‘distress’ is negative and results in damage to health (Selye, 1975). Secondly, Selye defined stress as a nonspecific response to noxious stimuli or to any demand or stressor but this pattern described as the general adaptation syndrome has been questioned by several authors as the evidence suggests that the psychophysiological response is more specific and also a single emotion such as anxiety could trigger differential responses depending on the person’s coping skills. Schachter (1957) demonstrated differential response to anger and fear. Similarly, Arnold (1945) reviewed the evidence of how emotional

states of fear, anger and excitement correspond to different physiological states. Fear demonstrates primarily adrenergic (sympathetic) effects and anger is primarily a cholinergic effect (parasympathetic). Thirdly, the definition does not consider cognitive factors such as appraisal of the situation. This is important because the response we now know depends on the meaning of stressor. Fourthly, the normative nature of nonspecific physiological response patterns does not allow for individual differences in perception of the stimulus or how a person uniquely copes with a threatening situation. Fifth, it is difficult to operationalise the stress response because of the dissociation between objective signs and the subjective experience (Lacey, 1967). Sixth the theory adopts an assumption that the response is general to all individuals which contradicts the philosophy that everyone is unique. There is limited empirical support for the nonspecific and uniform response to noxious stimuli in humans but there is abundant evidence that a person's perception of an event, his or her coping behaviours and physiological correlates do vary (Erikson & Ursin 2006).

### **Stimulus based definition of stress (Engineering approach)**

This definition of stress takes an objective view that *stress happens* to man as a result of an external environmental stimulus, for example adverse living conditions. The notion originates in physics (Lazarus, 1999). Here stress is defined as the force per unit area applied to a material either to stretch or compress it. The maximum stress a material can tolerate is known as breaking point. Strain is a measure of how much the material is stretched or deformed and this occurs in response to stress. In certain materials there is a linear relationship between stress and strain and there is a point where the stress can no longer be tolerated causing the object to break (Sang, 2010). On extrapolating this to humans, stressful stimuli produce strain which leads to a reaction akin to the distortion seen in materials. The linear relationship of stress and strain suggests that it is cumulative stress that eventually then leads to ill health and also that humans can tolerate strain to a degree.

This approach heavily focuses on the external environment and as such does not consider the internal and psychological components. However, the simplicity of this model has been useful in scientific research of stress and life events which can be seen as external environmental stimuli.

## Interactional and transactional definition of stress (Psychological approach)

This model was proposed by Lazarus and Folkman in 1984. It seeks to view the interplay of variables in the intermediate environment and those within the person and that both affect one another, the interaction. As such it is a combination of the view that stress *happens in man and to man*. However, the meaning a person constructs from the interaction operates at a higher-level thinking process and this can be explained by the term transaction. This is an appraisal by the person of the situation they find themselves in and what it signifies for their personal wellbeing. This analysis is dependent on how the person views what is happening which is in turn based on their individual goals, beliefs, personal resources and psychological characteristics which have formed from an interaction of biological origins and developmental experiences. Psychological harm can also occur when a person is expected to manage the demand with limited resources. Due to confusion between the two terms Lazarus states in his 1999 book on stress and emotion: a new synthesis, that it is better to use the term ‘relational meaning’ as this is construed by the person and used widely in psychology to understand individual differences.

In all the models stress is seen primarily as one of three components of the stress process: events or stressors, the inner state of the organism as a manifestation of the stressor or a person’s perception based on an appraisal for the situation.

### Box 3. Key Points: Explanatory models

- Three models can be used to explain stress; physiological, engineering and psychological. These view stress primarily as an internal response, external stimulus and an interaction between the individual and environment respectively.
- The models of stress overlap and clinically all aspects should be considered however for the purposes of research it can be useful to compartmentalise into these components.
- Of late there has been increasing interest in why some are more prone to stress than others which has widened the field of research into personality.

The components of stress are inseparable however studying them as separate entities has helped in focusing on each factor in depth, for example life event research has helped in identifying significance of life events contributing to ill health. Similarly, individual variability to experience stress has resulted in identifying different personality types and studying the interaction between environment and

individual has resulted in identifying the cognitive appraisal models and coping strategies.

The bio-psychological aspect of processing and response to stress is dealt with in more detail elsewhere in the book (in the chapters biological aspects of stress and psychological aspect of stress).

## **CLASSIFICATION OF STRESS**

Like the definition of stress, the classification of stress is also difficult due to conceptual issues. However, attempts have been made to classify stress and these depend on the theoretical orientation of the classifier and their research question. In the following section we have attempted to provide a framework for classification which has clinical utility.

In general, the classification of stress is based either on A) Stressors (or stimuli) or B) Stress response which is the consequential manifestation of stressors. Although arbitrary, the objectivity of this type of classification has several advantages as both the stressors and response can be easily identified, as such as it allows the possibility of discrete variables to be studied, these can be done qualitatively or quantitatively and also correlated with illness. It also has application in clinical practice when looking at which has manifested as predominant complaint in the person.

### **A) Stressor (or stimuli)**

The stimuli may be physiological (illnesses such as chronic medical conditions, cancer), psychological (personality), social (life events) or environment (occupational or personal).

The most studied stimuli are life events. As defined by the Oxford English dictionary these are an event in a person's life specifically a significant event that causes major change in a person's life, such as marriage, the birth of a child etc. Life events can be classified in several ways based on predetermined criteria. Holmes and Rahe (1967) in their social adjustment scale suggest weightings for the stressfulness of an event based on the responses of 394 subjects who were asked to rate the events compared to marriage which was given an arbitrary score of 500, asked to consider if the particular event resulted in more or less adjustment than marriage. The events chosen were empirically derived from clinical experience.

Life events can be seen as positive or negative based on the normally expected outcome from the given events for example a job promotion or birth of a child is often viewed as a positive life event and bereavement a negative life event. Another example is exit and entry events based on transition between roles and status based on the loss or gain from the change. The quality of the experience within the role will determine if the transition is uplifting or stressful (Pearlin, 2009)

The stimulus-based classification can also be viewed by the nature and severity of stressors, using the categories of routine stress, acute stress and traumatic stress. Routine stressors also called ‘daily hassles’ include ordinary life circumstances such as the pressure of work, family life and social activity but elements of which are perceived as unwanted, difficult to cope with or as having a lack of resources to cope. The role of this was popularised by DeLongis et al., in 1982 who demonstrated that life hassles were positively correlated with somatic illness.

Acute stressors are experienced commonly in everyday life. They result from the demand of recent or anticipated events in the near future. These are often but not always unexpected, examples include the loss of a job, divorce or separation and working towards a deadline. These stressors are often short lived and can be easily resolved.

Traumatic stressors are events, which pose threat to the physical and psychological integrity of an individual such as a major accident, assault, natural disaster, war etc. events like this may result in serious harm or even death (Calhoun & Tesdeschi 2006).

### **B) Stress Response:**

This is based on the nature and duration of the response. The American psychological association classifies stress response into three categories; acute stress, episodic acute stress and chronic stress.

The acute stress response is the most common stress response and is to the demands and pressures of recent past events and anticipated future events and it is usually easily recognised by the person. It can affect anyone but can often be easily managed. It is short lived and as such the physiological and psychological responses do not result in significant consequences.

The physical symptoms noted by Hans Selye (1950) in his work are due to activation of autonomic nervous system and the psychological symptoms are due to the interpretation of the stressors as described by Richard Lazarus (1999) in his theory of transaction. The symptoms of the stress response for an individual are unique and probably depend on the sensitivity of different organs to changes in the autonomic nervous system. It may be predominantly cardio-respiratory in some and gastrointestinal or genitourinary in others. Some may respond with sleeplessness, irritability, self-destruction, anger, violence and so forth, some of the features often noted in the medical diagnostic criteria of stress disorders in the international classification of disease and the diagnostic and statistical manual of mental disorders.

The common manifestations are due to increased sympathetic activity affecting different systems (Cannon, 1915) and these are summarised in table 1.

**Table 1: Common symptoms arising from the acute stress response**

System	Symptoms
Musculoskeletal	tension resulting in aches and pains
Psychological	irritability, anger, anxiety, depression
Cardio-Respiratory	dizziness, palpitations, sweating hyperventilation
Gastrointestinal	dry mouth, nausea, diarrhoea
Genito-Urinary	incontinence

Episodic acute stress as the phrase suggests that it is a form of recurrent stress. This is often seen in people whose lives are disorganised and experience frequent crises as a result. It is common in people with low frustration tolerance. They habitually respond with panic, anger or frustration. They are usually over aroused, short tempered, anxious or chronic worriers. Their pattern of response is ingrained in their lifestyle and they are usually resistant to change. This may often reflect personality rather than the nature of the situation. Cardiologists Meter Friedman and Ray Rosenman (1976) described Type A personality characterised by excessive competitive drive, impatience, hurriedness and aggressiveness. Persons of this personality are more prone to episodic acute stress and are also more prone to cardiac events. The symptoms are similar to acute stress but experienced frequently and for a longer period.

The chronic stress response is to the unrelenting demands and pressures that are seemingly interminable, and the person believes that they have little control over. Examples include poverty, a dysfunctional family life, living in unhappy relationships, unemployment, dissatisfaction with one's career and living in political conflict areas. The manifestations of chronic stress are often difficult to recognise and treat. Many people may get used to chronic stress but its effects on their lives will remain and tend to manifest as physical and mental illnesses including suicide and personality problems. Chronic stress during childhood may have profound effects on the development of personality (Paris, 1997) and a person's outlook on life for example having an automatic lack of trust in others and the general view that the world is dangerous. These views and behaviours are often so ingrained that people with chronic stress require long term medical and psychosocial intervention to make major changes in their life.

**Table 2: The main differentiating features between the acute and chronic stress response**

Acute Stress response	Chronic Stress response
Rapid onset	Insidious onset
Short duration	Long lasting
Severe course	Recurrent course
Initial response is usually without conscious awareness with flight, fight or freeze responses	Response is subtle and may or may not be with conscious awareness with varied responses
Aimed at survival	Aimed at managing
Predominant sympathetic hyperactivity	Predominant hypothalamic-pituitary-adrenal axis activation
May boost immune response	Suppress immune response
Difficult to prevent and may be easier to treat	Easier to prevent and may be difficult to treat

The acute stress response is usually quick, and the body responds with flight, fight or freeze as soon as the situation is recognised as a threat even before the situation reaches the conscious mind. It activates the survival mechanism and various systems such as the autonomic nervous system and immune system to divert the metabolic activities from activities less important for immediate survival such as digestion, sleep, reproduction etc to survival activities such as mental

arousal and rapid refocusing, running and fighting. The body will return to baseline functioning once the acute or traumatic stressor is removed or managed.

The chronic stress response is subtle, and the person may not be consciously aware of it. The body response is slower without emotional flashlights or physical red flags making it harder to detect. The response may go on for years and even decades without conscious awareness causing slow but serious harm to several organ systems. Hans Selye (1946) described the physiological manifestations as a result of heightened hormonal and chemical levels as the disease of adaptation which include hypertension and the formation of gastric ulcers.

However, unlike in the acute stress response in which body returns to normal functioning once the stressor is dealt with, in chronic stress response the body does not return to normal functioning because the source of the stressors still persist as they are in the person's everyday life. Such stressors may have serious health consequences if they persist in the long term because the resulting physiological changes as seen in the acute response persist and can predispose to illness such as hypertension, diabetes, heart disease and mental illness. These issues are dealt with further in the chapter on the biological effect of stress on bodily functions.

The modern illnesses without known causes are etiologically linked to stress which in turn is a product of modern lifestyle. Even susceptibility to infection is thought to be a function of environmental conditions culminating in physiological stress on the individual rather than simple exposure to external sources of infection.

### Box 4. Classification of stress: key points

- There is no universally accepted classification for the stress
- Broadly this can be viewed in two categories: stressors and the stress response
- The stress response can be classified as acute, chronic or episodic depending on the duration.
- The responses elicited are universal but not inevitable in all and are therefore unique to the individual.
- Those under chronic stress may be more prone to experience physical illness such as ischaemic heart disease, hypertension and repeated viral infections.

## NEW TRENDS

Over several decades of research on stress, there has been increasing recognition of positive and preventative aspect of stress. It is beyond the scope of the chapter to delve into extensive review on the subject. In the following section, we have highlighted a few examples indicating several directions the stress research could take in future

### **Post- stress growth and post- traumatic growth**

The initial research on stress predominantly focussed on the negative physiological and psychological manifestations of this. However, the notion that stress can lead to positive change dates to ancient ways of life and is a forefront of many religions. For example, the suffering of Jesus Christ is central to most branches of Christianity and Greek drama was often centred around tragedy and the transformation of characters after experiencing traumatic events (Calhoun, 2006).

Though Caplan theorised in 1964 that negative life experiences or crises are the potential for growth it was in the late 80s to 90s that research really began to focus on growth related to stress. Park et al., (1996) developed the stress related growth scale in an attempt to quantify this growth. The amount of personal growth experienced was measured using a rating scale with items such as “I learned not to let hassles bother me the way they used to” and “I learned to work through problems and not just give up”. They found that the scores on the scale were positively correlated with the participants ratings of the negative events initial and current stressfulness. As such demonstrating that growth results from life crisis.

### **The prenatal environment**

Factors leading to stress related to mental health can be traced back to the prenatal environment. It is widely accepted that an adverse early environment such as malnutrition, is indicated by small size at birth. Thus, this marker can be used to study the impact of the foetal environment on stress and this is a developing field and mechanisms but which these environmental exposures operate to change bio behavioural stress mediates are not fully understood.

There is evidence that low birth weight is linked to an enhanced physiological response to stress looking at parameters such as blood cortisol levels, blood pressure and heart rate (Phillips, 2008). Low birth weight has also been associated with increased susceptibility to stress in several small studies. (Lundgren et al. 2001;

Nilsson et al. 2001). Nilson showed that in a cohort of 90,561 Swedish conscripts scores on psychological functioning including stress susceptibility, based on semi-structured interview continuously improved up to a birthweight of 4200grams. Thereby adversity in utero can be seen to increase stress reactivity which in turn is a vulnerability factor for mental illness (Myin-Germeys et al. 2003).

### **Stress belief**

This alludes to how people view stress, with origins in the eustress concept described by Selye (1975). Stress can be seen as good for people and a way of getting ready for action, a driving force to motivate us to learn, achieve goals and get things done. Examples include studying for exams and learning to pass a driving test. Some people find that they thrive in high stress environments. Working towards an outcome can make people focus their energy and lead to creativity as well as personal growth.

However, this type of stress can become problematic if it persists over a longer period than anticipated or becomes viewed as negative or results in physical manifestations.

#### **Box 5. Key Points: New trends**

- Stress research has predominantly focussed on the negative aspects of this. However, there is growing research and a wider accepted view that stress can be positive and conducive to personal growth.
- There is a strong individual component to the perception and manifestation of stress, and it is possible part of this is influenced by the prenatal environment.

## **THE SPECTRUM OF STRESS: FROM UNDER STIMULATION TO TRAUMA**

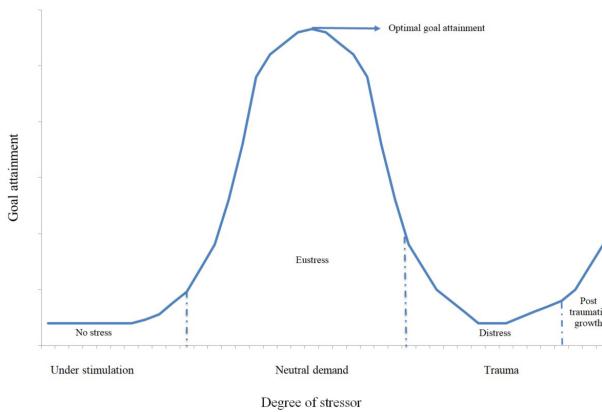
It is clear from our discussion above that stress is a process consisting of stressor in the environment, the individual processing of the stressor and the response or manifestation of it. In the following section we have examined the idea of stressors on a spectrum from under stimulation to trauma, which has been depicted in Figure 1.

As the concept of stress is so broad many things can be subsumed under the term stress without any differentiation of life difficulties, demands and trauma. However, it is important to consider the context of the stressor and differentiate

the degree of stimulation and at which point this translates to stress. Stimulation or stressors as challenges during the developmental stages of life is good for future stages of life. If the stressor is predictable and the individual has control over it and it is of moderate severity, it can result in development of resilience. If the stressor is unpredictable and there is no control on the part of the individual and or it is severe, it can result in distress and then negative consequences such as suffering, onset of mental illness and development of chronic medical conditions.

In the middle of the spectrum is a neutral challenge or demand, one which can be useful in motivating a person to utilise their full potential to achieve their goals. Thus, this type of demand improves performance and achievement. It is common experience that an individual performs to their best potential if they have a goal. The motivation to achieve a goal is high if the goal has a tangible outcome. Preparing for an examination is a good example in which stress to a degree is useful to obtain the desired result. However, a person experiences stress if the pressure to achieve goes beyond one's ability to cope. Richard Lazarus (1999) in his interactional-transactional model describes how threat arises 'when a person with an important goal faces an environmental condition that endangers the attainment of that goal'.

**Figure 1. The spectrum of stressors and the relationship to goal attainment.**



Under stimulation leads to limited attainment of goals if any. Neutral demands, also seen as good stressors, can motivate and energise someone to perform optimally towards achieving their goals. Trauma can result in ill health and as such hinder achievement of goals, however post traumatic growth can ensue. The level

of stress response to the stimulation or stressor within the person can also be seen on a spectrum from no stress to eustress to distress.

Similarly, a lack of stress or demand leads to underperformance as there is no or little stimulation to achieve goals if any , this is often seen in people with severe mental illness. In these situations, a person can experience amotivation and a diminished social life resulting in under fulfilment in life.

Is trauma an extreme form of stressor? The answer to this can be approached in two ways. Although trauma and stressor are seen as single entities, they are conceptually different both in quality and quantity. In contemporary understanding broadly a stressor is a common place demand but is beyond one's ability to cope resulting in stress. However, trauma can be seen as much more than a stressor because it is beyond the ordinary life experience. It can be unexpected, dramatic, life threatening and is certainly more significant to the person than the difficulties experienced in routine life, for example the sudden loss of a loved one. It is often the unexpectedness of the event that makes the experience traumatic. Those events that are normally expected such as everyday hassles, though not desirable in the individual's life can be seen as non-traumatic stressors although some may have traumatic qualities.

Trauma can also be approached as an extreme form of stressor as opposed to a separate entity. As noted above in certain literature stress is described as any challenge or demand on physiological and psychological functioning, requiring the homeostatic mechanism to adjust outside the normal dynamic activity. Traumas such as severe accidents, rape or physical assault are events that threaten physical or psychological integrity of the individual. Some traumas such as sexual assaults and physical assaults resulting in loss of bodily functioning for example loss of limb or vision is the ultimate experience of helplessness a person can endure.

From the physiological point of view dramatic, rapid, unpredictable events activate the body systems to deal with the effect of the event through various neuronal and hormonal systems of the body. These systems activate compensatory mechanisms for the body to cope with the extra challenge. However, such efforts of the body response works very well in acute stressful situations however if the stress persists and becomes chronic it causes the body to set up a new system to bring the

homeostasis back. The new system helps the organism to survive the trauma but at the expense of compromising the full functional capacity of the organism.

An individual's ability to cope with the extra demand depends on the nature of the demand and their reserves and experience. For example, a young individual may cope with extra physical demands on the body, but she may find it difficult to cope with extra emotional demand on the psyche. Similarly, an older person may cope better with extra emotional demand as they may more readily solve a problem but may not cope with extra physical demand. As the body's physical reserve will decrease as the person gets older while his emotional resilience and problem-solving ability improves with experience of life and exposure to difficulties in life. Therefore, a young person may develop better resilience if he is exposed to challenges in life and which may help to cope with demands of life better as they get older.

#### Box 6. Key Points: The spectrum of stress

- Stressors can be viewed on a continuum from under stimulation to trauma and lastly post-trauma.
- The perception of where a stimulus is on the spectrum depends on the individual based on a wide array of factors including physical health status and personality.
- Extremes of the spectrum can both have adverse consequences for the individual and can lead to an impoverished quality of life due underachievement and illness.

## CONCLUSIONS

With hindsight it is clear that adversities were what would constitute stress in the 14th century. However, the concept was unheard of until the early 20th century at which point delineation of different aspects of stress began. There remain difficulties in defining stress, but this has been overcome to a degree by developments of models of stress and classification systems.

Whilst initially it was largely negative physical and psychological aspects of the stress process that were studied, more recent research has moved towards positive aspects such as eustress and post traumatic growth. Studies into perinatal and childhood factors provide the potential for preventative strategies to reduce the negative stress response. Future studies may take several directions however the most likely trajectory would be in the direction of positive and preventative aspect of stress.

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## **BIOLOGICAL EFFECTS OF STRESS ON BODY FUNCTION**

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**OUTLINE**

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|---|--|
| 1. INTRODUCTION                                 | 2. WHAT IS STRESS?                                   |
| 3. IMPACT OF STRESS ON THE BODY AND ITS SYSTEMS | 4. STRESS DURING EXTREMES OF LIFE: INFANCY AND AGING |
| 5. STRESS THROUGH THE AGES- FOOD FOR THOUGHT    | 6. CONCLUSIONS                                       |

### **INTRODUCTION**

All forms of life, during one or the other time, encounter what we simply term as “stress”. Be it in the form of a written examination or presenting a symposium, a job interview or the final hours before your wedding, being given the news of a serious medical illness of your loved one or narrowly escaping a near-death experience-the same butterflies fly in your stomach during each of these times. While one may be able to compress the effects of these stressful situations or stressors to what is seen externally, there is in fact, a myriad of events taking place in the body.

### **WHAT IS STRESS?**

So, what is stress? The word, “stress” was coined by Hans Selye in 1956, who defined it as “the non-specific response of the body to any demand,” (Selye, 1956). As per Levine, “Stress may be defined as a real or interpreted threat to the physiological or psychological integrity of an individual that results in physiological

and/or behavioural responses”, (Levine, 2005). Chrousos and Gold (1988) define stress as “the state of threatened balance, equilibrium or harmony. The adaptive response can be specific or can be generalized and non-specific.”

**Box 1: Definitions**

**Stressor:** A stressor is any stimulus, agent, event or situation that causes stress to an individual.

**Homeostasis:** Homeostasis is a self-regulating process by which biological systems maintain stability while adjusting to changing external conditions (Billman, 2020). It is a dynamic process through which one can maintain a steady or stable internal state in order to adapt and survive to adverse situations.

Over the years, the definition of this word (i.e. ‘stress’) has undergone constant modification to suit different contexts but has maintained an overall unfavourable undertone. Contrary to this belief, stress can be both- positive, also known as ‘eustress’ and negative, also called ‘distress’. Hence, the effects of stress on the body can similarly be both positive and/or negative depending on several internal and external factors (Levine, 2005).

As shown by the stress-response curve below (figure 1), with an initial increase in stress, the performance of an individual increases thereby leading to personal growth and productivity. The graph continues to rise reaching the stage of optimal activity achieved by an individual; further stress now serves as distress leading to physical fatigue, mental exhaustion and ill health. The term “hypostress” is also used in the graph which is insufficient stress leading to under-challenging and boredom for an individual. Similarly, “hyperstress” is an excessive amount of stress that often pushes one beyond his/her capabilities (Nixon et al., 1979).

When we look at the relationship between stress and homeostasis, an inverted U-shaped dose-response curve is obtained (figure 2). Basal homeostasis (or eustasis) is achieved in the central, optimal range of the curve while suboptimal effects is seen on either sides of the curve which can lead to insufficient adaptation, a state that has been called allostasis (different homeostasis) or, more correctly, cacostasis (defective homeostasis, dyshomeostasis ,distress) (Chrousos, 2009). This ultimately leads to pernicious effects on the organism, both in the short term as well as in the long term.

Figure 1: The Stress-Response Curve (Adapted from: Nixon et al., 1979)

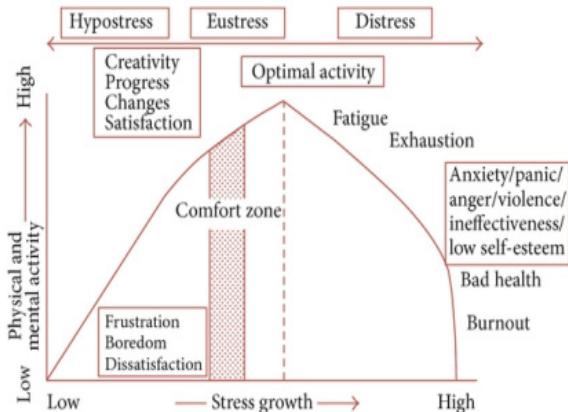
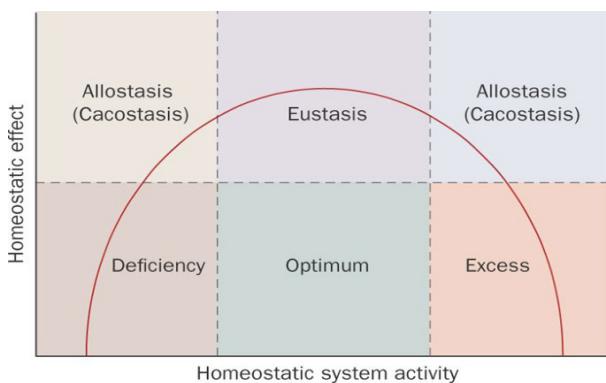


Figure 2: Homeostatic systems exert their effects in an inverted U-shaped dose response (Adapted from: Chrousos, 2009)



### Box 2: Stress Mindset Theory

Interestingly, the effects of stress on the body and our response to it also depend on our mind or quite literally, as we perceive stress to be! Stress mindset is conceptualized as the extent to which an individual holds the mindset that stress has enhancing consequences for various stress-related outcomes (referred to as a "stress-is-enhancing mindset") or holds the mindset that stress has debilitating consequences for outcomes such as performance and productivity, health and well-being, and learning and growth (referred to as a "stress-is-debilitating mindset") (Crum et al., 2013).

While the effects of eustress play a pivotal role in an individual's life ultimately resulting in salubrious effects on the body and mind, it is distress that is often overlooked by one leading to steady deterioration of one's health and an imbalance of the internal milieu. Hence, to effectively combat with the deleterious effects of stress on the body, one must first identify and understand the same.

## **IMPACT OF STRESS ON THE BODY AND ITS SYSTEMS**

### **Nervous system**

The nervous system mainly comprises the central nervous system and the peripheral nervous system. The central nervous system includes the brain and the spinal cord while the peripheral nervous system involves the autonomic and somatic nervous system. With reference to the regulation and response to stress, both central (that influences the hormonal secretion) and peripheral (autonomic) play a role. In 1968, McEwen suggested for the first time that the brain of rodents is capable of responding to glucocorticoid (as one of the operators in the stress cascade). This hypothesis that stress can cause functional changes in the CNS was then accepted (McEwen et al., 1968).

### **Memory**

The total function of memory and the conversion of short term memory to long-term memory are dependent on the hippocampus; an area of the brain that has the highest density of glucocorticosteroid receptors and also represents the highest level of response to stress (Scoville & Milner, 1957; Asalgoo et al., 2015).

Chronic stress and, consequently, an increase in plasma cortisol, leads to a reduction in the number of dendritic branches (Woolley et al., 1990) and the number of neurons (Sapolsky et al., 1990), as well as structural changes in synaptic terminals (Sapolsky et al., 1990) and decreased neurogenesis in the hippocampus tissue (Gould et al., 1998). Glucocorticosteroids can induce these changes by affecting the cellular metabolism of neurons (Lawrence & Sapolsky, 1994), increasing the sensitivity of hippocampus cells to stimulatory amino acids (Sapolsky & Pulsinelli, 1985) and/or increasing the level of extracellular glutamate (Sapolsky & Pulsinelli, 1985). Additionally, adrenal steroids lead to alteration in long-term potentiation (LTP), which is an important process in memory formation (Bliss & Lømo, 1973). Supporting evidence shows that people with either Cushing's syndrome (with an increased secretion of glucocorticosteroids), or people who receive high dosages of exogenous synthetic anti-inflammatory drugs, are observed to have atrophy of the

hippocampus and associated memory related problems/disorders (Ling et al., 1981).

Additionally, two factors are involved in the memory process during stress. The first is noradrenaline, which creates emotional aspects of memories in the basolateral amygdala (Joëls et al., 2011). Secondly, this process is facilitated by corticosteroids. However, if the release of corticosteroids occurs a few hours earlier, it causes inhibition of the amygdala and corresponding behaviours (Joëls et al., 2011). Thus, there is a mutual balance between these two chemicals for creating a response in the memory process.

Glucocorticoids produce effects in the brain both genomically and non-genomically via multiple sites and pathways, and they have biphasic effects in which the timing and the level of glucocorticoid response (GR) expression are critical (Joëls, 2006; Popoli et al., 2012). The level of expression of glucocorticoid receptors is very important. Genetically induced over-expression of GR in forebrain leads to increased ability of mood related behaviours and yet also confers greater responsiveness to antidepressant drugs (Wei et al., 2004). Genetically induced under-expression of GR has the opposite effect (Jacobson, 2014). Epigenetic mechanisms such as the increased CpG methylation within the GR promotor is associated with a sluggish Hypothalamic-Pituitary-Adrenal (HPA) stress response and is associated with poor maternal care in rodents and early life abuse in human suicide victims (Syzf et al., 2005; McGowan et al., 2009).

### Box 3: Epigenetics

"Epigenetics" refers to events "above the genome" that regulate expression of genetic information without altering the DNA sequence. Mechanisms include DNA methylation, histone modifications that repress or activate chromatin unfolding (Allfrey, 1970) and the actions of non-coding RNA (Mehler, 2008) as well as transposons and retrotransposons (Griffiths & Hunter, 2014) and RNA editing (Mehler & Mattick, 2007).

It is when nature (epigenetic modifications) interacts with nurture (environmental influences and life experiences), do we see the unique traits between individuals in their response and adaptation/maladaptation to stress. These environmental influences can result in healthy or unhealthy brain architecture and in epigenetic regulation that either promotes or fails to promote gene expression responses to new challenges (McEwen, 2017). This can be made evident by twin study findings

such as, identical twins diverge over the life course in patterns of CpG methylation of their DNA reflecting the influence of “non-shared” experiences (Fraga et al., 2005).

Another example of how genetics plays an important role in adaptation to stress is seen by how different alleles of commonly occurring genes determine the way individuals respond to experiences. For example, the short form of the serotonin transporter is associated with a number of conditions such as alcoholism, and individuals who have this allele are more vulnerable to respond to stressful experiences by developing depressive illness (Caspi et al., 2003; Spinelli et al., 2012). As shown, these alleles may lead to successful outcomes if exposed to a positive and nurturing environment, while lead to adverse outcomes if one is exposed to early stressful environment. This has led them to be called “reactive or context-sensitive alleles” rather than “bad genes” (Boyce & Ellis, 2005; Suomi, 2006; Obradovic et al., 2010).

#### **Box 4: Survival of the sharpest!**

It cannot be emphasized that not all stress is bad for our mind or in this case-memory. In certain situations, our mind is sharpened when it perceives to be in a threatening environment or unfamiliar circumstances that may have an unpredictable outcome; this leads to better adaptability and response.

Hence, ultimately the timing of exposure to stress, total duration of stress and emotional condition of an individual can together make an impact on memory—either for the better or for the worse.

### **Cognition**

Mild stress facilitates an improvement in cognitive function, especially in the case of virtual or verbal memory. This is often encountered by one before a viva-voce examination or a difficult memory game played in a group. However, cognitive disorders especially in memory and judgment can occur if the intensity of stress passes beyond a predetermined threshold (that varies within individuals). Activation of the central and autonomic nervous system are influenced by stress which also has an impact on the HPA axis. Together, these three have a role in neural circuits that involve data processing. Stress has effects on cognition both acutely (through catecholamines) and chronically (through glucocorticosteroids) (McEwen & Sapolsky, 1995). Acute effects are mainly caused due to beta-adrenergic effects, while steroids induce long-term effects through changes in gene expression.

Furthermore, the lipophilic properties of glucocorticosteroids enable their diffusion through the blood-brain barrier through which it can also exert long-term effects on processing and cognition (Sandi, 2013).

Chronic stress can cause complications such as increase in Interleukin (IL-6) and plasma cortisol and decrease in amounts of cAMP responsive element binding protein and brain-derived neurotrophic factor (BDNF), which is very similar to what is observed in people with depression and mood disorders that exhibit a wide range of cognitive problems (Song et al., 2006).

## **Sleep**

Stress and sleep share a close link with each other. Persistent stress leads to difficulty in falling asleep and poor sleep quality. Chronic sleep deprivation can further lead to increase in stress and poor coping mechanisms to combat with the same creating a vicious cycle of distress. Mediators of stress such as CRH (corticotrophin releasing hormone), cortisol and norepinephrine suppress the sleep system and causes insomnia and daytime somnolence (Chrousos, 2009). Insufficient night sleep and excessive day time sleepiness subsequently lead to impaired role functioning. Hence, this vicious cycle is propagated leading ultimately to other mental and physical health problems. These secondary health problems (such as fatigue, headache, GI symptoms such as indigestion, lowered immunity leading to infections, etc) may also then interfere with sleep.

## **Autonomic system**

The autonomic response is considered to be the immediate or first phase response to a stressful situation which involves appraisal of stress and adaptation to the same. This is a more reflexive mechanism that aids and prepares the individual to be more vigilant to the threat and is usually short lasting (Ulrich-Lai & Herman, 2009).

Table 1 below summarizes the effects of the sympathetic system on various organ systems of the body that occur during a stressful situation leading to the “fight or flight” response; the parasympathetic system that has opposing effects on the body is involved during the resting state of an individual and also to restore the same after cessation of the stressful stimulus, appropriately earning the title, “rest and digest”. These effects are mediated through two main neurotransmitters- norepinephrine and acetylcholine amongst others (Chrousos, 1997).

**Table 1. Effects of the sympathetic and parasympathetic system on the body**

<b>Organ</b>	<b>Sympathetic system</b>	<b>Parasympathetic system</b>
Pupils	Dilatation	Constriction
Salivary glands	Saliva reduction	Saliva production
Sweat glands	Increased sweating	No change
Adrenal gland (adrenal medulla)	Release of adrenaline and noradrenaline	No effect
Musculoskeletal system	Muscular contraction	Muscular relaxation
Heart	Increased heart rate and contractility	Decreased heart rate and contractility
Lungs	Bronchodilation	Bronchoconstriction
Gastrointestinal tract	Decreased motility (peristalsis)	Increased motility
Liver	Increase in conversion/ breakdown of glycogen to glucose	Increased glycogen synthesis
Kidney	Decreased urine output	Increased urine output
Bladder	Contraction of sphincter	Sphincter relaxation

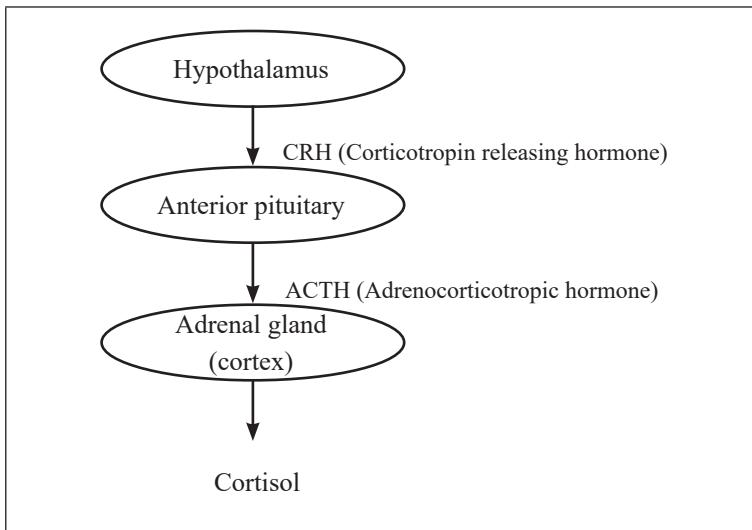
### **Hypothalamic-Pituitary-Adrenal Axis (HPA axis)**

As opposed to the response shown by the sympathetic autonomic system, the effects of the HPA axis are less rapid but longer lasting, constituting the secondary response that is activated when appraisal of a stressful stimulus is made (Joëls & Baram, 2009). During stress, the autonomic system and the HPA axis interact with each other in multitudinous ways and complement each other.

As mentioned above, the HPA axis plays a crucial role in an individual during stress. The resultant effect on stimulation of this axis is an increase in the circulating glucocorticoids (cortisol). In figure 3 shown below, one can see the hypothalamus releasing CRH which in turn, stimulates the anterior pituitary gland to secrete ACTH. ACTH stimulates the adrenal cortex to release cortisol which by negative feedback mechanism suppresses the hypothalamus and the anterior pituitary gland thereby playing a regulatory role in the basal control of the HPA axis (Chrousos

& Gold, 1992). Through this feedback inhibition, the effects of glucocorticoids on tissues can be regulated.

**Figure 3: The HPA axis**



Glucocorticoids are steroids that exert its effects on a variety of cells through abundant intracellular receptors. After translocating to the nucleus through ligand binding and dissociation, they combine with glucocorticoid responsive elements (GREs) of the genome and activate hormone responsive genes that inhibit transcription factors and may reduce protein translation rates which are involved in the growth and function of immune and non-immune cells (Chrousos, 1997). Glucocorticoids are mainly involved in body functions such as immunosuppression, anti-inflammation, lipogenesis, protein catabolism and bone resorption. The harmful effects it exerts during stress will be dealt under appropriate headings.

### **Immune system**

Hans Selye had performed a series of experiments on rats and had come up with the term, “General Adaptation Syndrome”. Based on his studies, rats on being exposed to noxious stimuli (cow ovarian extracts, exposure to cold, muscular exercise, drugs) showed a set of non-specific findings irrespective of the stressor stimuli (Tan & Yip, 2018). These were mainly: adrenal gland hypertrophy, atrophy of the lymphatic system including the thymus, and peptic ulcers of the stomach and

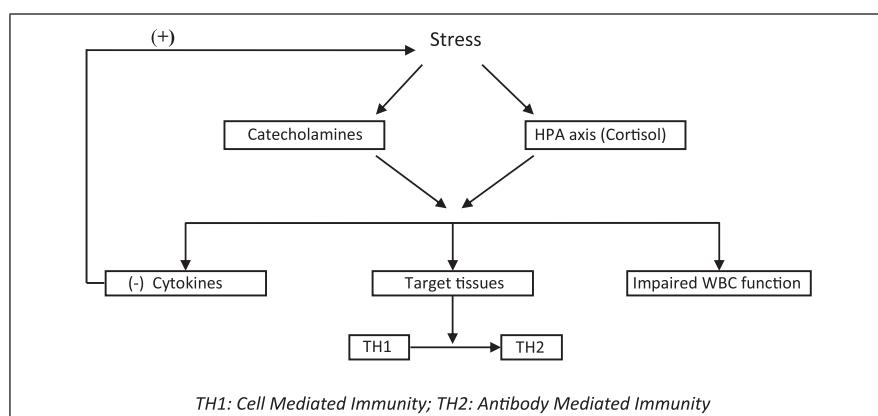
duodenum (Tan & Yip, 2018). Selye's syndrome can be extrapolated today to the dysfunction in immune and GI system due to stress.

**Box 5: General Adaptation Syndrome (GAS)**

The General Adaptation Syndrome divides the total response attained due to stress into three phases: (1) alarm phase, characterized by acute manifestations as they are taken off guard initially; (2) resistance phase, when the acute manifestations disappear as the organism tries to resist the change; and (3) exhaustion phase, when first stage reaction may be present again or when it may lead to exhaustion and collapse of the organism (Selye, 1936; Tan & Yip, 2018).

Glucocorticoids and catecholamines suppress the secretion of proinflammatory cytokines such as tumour necrosis factor (TNF) and interleukins (IL-1, IL-6, IL-8 and IL-12) and also interfere with the function of leukocytes, thus playing a major role in inferring immunity (Karaklis et al., 1991; Chrousos, 1995; 1999; Elenkov et al., 2008). They affect both types of immunity i.e. cell-mediated immunity (TH1 response) as well as the antibody-mediated immunity (TH2 response) by inducing a systemic switch that converts the former into the latter (Karaklis et al., 1991; Chrousos, 1995; 1999; Theoharides et al., 1995; 1999). On the other hand, proinflammatory cytokines stimulate the stress system at multiple levels including the central as well as the peripheral nervous systems. This leads to a rise in the level of glucocorticoids which then suppresses the inflammatory cascade of events as mentioned above. Thus, this serves as a crucial negative feedback loop that protects an individual from an overdrive of the inflammatory response (Chrousos, 2009).

**Figure 4: Stress and immune system**



At the peripheral level, the post ganglionic neurons secrete CRH while interleukin-6 (an inflammatory cytokine) is released by other peripheral immune cells due to activation of norepinephrine. This subsequently leads to degranulation of mast cells which releases inflammatory molecules from their secretory vesicles at various tissue sites (Kalaris et al., 1991; Chrousos, 1995; Theoharides et al., 1995; Elenkov et al., 2008). Depending on these tissue sites, a plethora of acute stress-induced disorders are given birth to when a susceptible individual encounters stress. For example, degranulation of mast cells taking place at the lungs would give rise to asthma and the same taking place in meningeal blood vessels would cause migraines. Similarly, CRH induced mast cell degranulation at the amygdala could trigger panic attacks (Kalaris et al., 1991; Theoharides et al., 1995; Elenkov et al., 2008). Chronic stress-induced disorders are explained on the basis of TH1 to TH2 switch which increases the possibility to develop TH2-driven autoimmune disorders (Frachimont et al., 2003). These include Grave's disease, systemic lupus erythematosus (SLE), certain infections and allergic conditions. A depressed immune system also gives rise to various skin disorders such as dermatitis (eczema) and exacerbation of psoriasis, malignancies and collagen tissue disorders to name a few.

### **Gastrointestinal system**

So how does one feel the butterflies in their stomach before delivering a speech in public or just before one is about to sky-dive? The gastrointestinal system has a brain of its own known as the enteric nervous system. In fact, the digestive tract is lined by the same neurons such as that found in the central nervous system and uses neurotransmitters such as serotonin to interact with the brain. The neurons detect or sense the entry of food into the gut and help in peristalsis which is a process by which passage of food occurs through the tract by muscular contractions (Goldstein et al., 2013).

The communication between the enteric and the central nervous system is bidirectional, linking the intestinal functions of the gut with the cognitive and emotional centers of the brain. This is known as the gut-brain axis (GBA). Recently, gut microbiota has been found to have an impact on this interaction, altogether forming the brain-gut-microbiome (BGM) axis (Carabotti et al., 2015).

Given below is a table briefly mentioning the mechanisms through which interaction between the brain, gut and microbiota occurs (Carabotti et al., 2015)

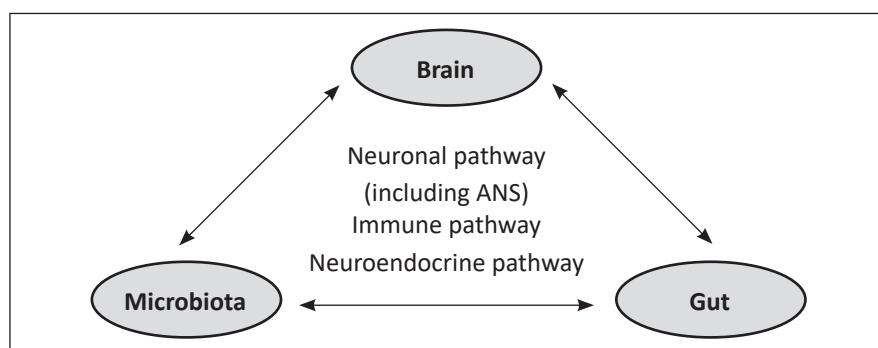
(Table 2). Various studies have shown evidence that stress induces a disruption in these mechanisms playing a pathophysiological role in a variety of gastrointestinal disorders such as irritable bowel syndrome, inflammatory bowel disease, gastroesophageal reflux disease (GERD), obesity as well as neuropsychiatric disorders such as anxiety, depression, autism spectrum disorders and Parkinson's disease (Cryan & Dinan, 2012; Martin et al., 2018).

**Table 2. Mechanisms of the BGM axis (Carabotti et al., 2015)**

From gut microbiota to brain:	From brain to gut microbiota:
<ul style="list-style-type: none"><li>• Production, expression and turnover of neurotransmitters (i.e. serotonin, GABA) and brain derived neurotrophic factor (BDNF)</li><li>• Protection of intestinal barrier and tight junction integrity</li><li>• Modulation of enteric sensory afferents</li><li>• Bacterial metabolites</li><li>• Mucosal immune regulation</li></ul>	<ul style="list-style-type: none"><li>• Alteration in mucus and bio-film production</li><li>• Alteration in motility</li><li>• Alteration of intestinal permeability</li><li>• Alteration in immune function</li></ul>

Figure 4 below shows a schematic representation of the bidirectional interaction of the brain-gut- microbiota and principle pathways associated with it.

**Figure 5: BGM axis and principle pathways**



According to American Psychological Association, during the time of stress, an individual may experience drastic changes in their appetite or food intake. While

some people may hardly be able to eat owing to stress, others may have an increased intake of food though not necessarily due to increase in appetite. Increased intake of food and/or increased intake of alcohol or tobacco which is often seen as a coping method in individuals lead to GERD and heartburn. Stress may also cause bloating, nausea or vomiting, if severe enough. Chronic stress leading to persistent decreased intake leads to weakness and weight loss (APA, 2018).

#### **Box 6: Good food equals good mood!**

Yes, that's right! A number of studies have shown that eating unprocessed and natural foods that are high in vitamins, minerals and antioxidants are beneficial for mental health. Probiotics and fermented foods that contain the "good bacteria" have improved mood by reducing feelings of depression and aggression. As per a Harvard health blog (Selhub, 2015), on nutritional psychiatry, 95% of serotonin is produced in the GI tract- the same neurotransmitter involved in regulating mood and pain, whose levels are also influenced by the good bacteria. Furthermore, a 25-35% reduced risk of depression was seen in those on Mediterranean and Japanese traditional diets containing unrefined and fermented foods.

### **Musculoskeletal system**

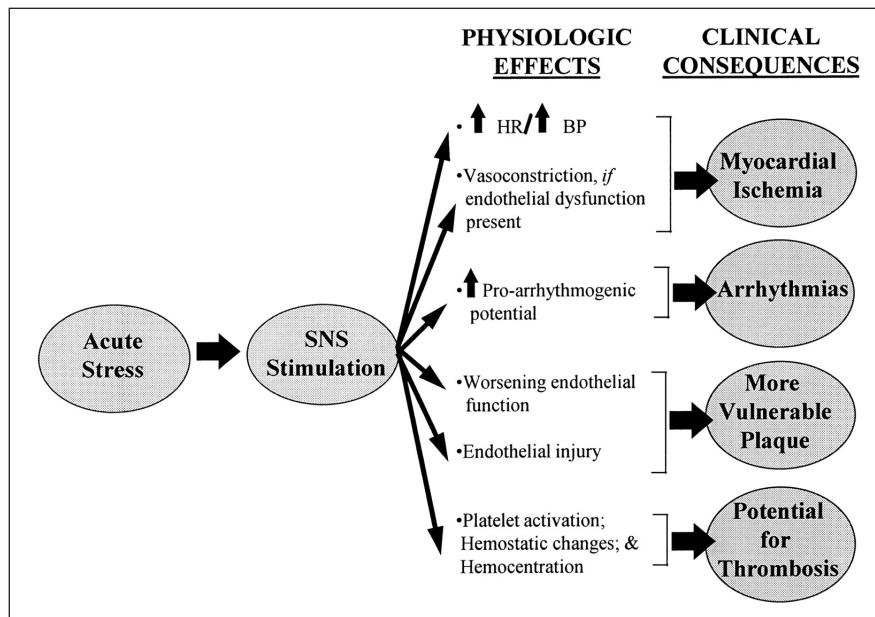
As seen in table 1, the sympathetic system causes muscular contraction which acutely prepares one for the flight and fight response. Chronic stress leads to a sustained state of muscular contraction that promotes other reactions and stress-related disorders. For example, tension-type headache and fibromyalgia is often associated with chronic muscular tension in the shoulders and neck. Disruption in the HPA axis that can occur due to stress has also been reported as an aetiopathological factor in Chronic Fatigue Syndrome (CFS) (Sadock & Ruiz, 2015). Various other autoimmune and inflammatory disorders such as rheumatoid arthritis, ankylosing spondylitis and osteoarthritis amongst others exacerbate secondarily due to damage caused by stress-induced inflammation and free radicals.

### **Cardiovascular system**

Acute effects of stress on the cardiovascular system are mediated by the sympathetic system though occasionally, the parasympathetic or vagal response is seen which leads to decreased contractility of the heart, peripheral vasodilation, decreased heart rate and blood pressure and ultimately, cardiac arrest. Faulty eating habits, smoking and chronic alcoholism as often seen in individuals coping with chronic stress leads to altered cholesterol levels, hypertension and coronary artery disease (Rozanski et al., 1999).

Figure 5 shows a schematic representation of the pathophysiology and clinical outcomes associated with stress on the cardiovascular system. The clinical consequences shown in the figure ultimately lay the foundation for more fatal sequelae such as myocardial infarction and sudden cardiac death (Rozanski, 1999).

**Figure 6: Schematic of pathophysiological effects of acute psychosocial stress**  
(Adapted from: Rozanski, 1999)



### Respiratory system

Many emotional and physical stressors increase ventilation in humans such as excitement, fear, exposure to sudden and long-term cold, heat, hypoxia, and severe pain (Cakmur, 2020). While this is a normal adaptive phenomenon in individuals without underlying respiratory problems, these physical and psychological stressors can exacerbate breathing problems for people with pre-existing respiratory diseases such as asthma and chronic obstructive pulmonary disease which include emphysema and chronic bronchitis (APA, 2018). As already stated before, a defective immune system further leads to exacerbation of asthma through CRH-induced mast cell degranulation. Furthermore, rapid breathing or hyperventilation caused by stress can bring on a panic attack in someone prone to develop the same (APA, 2018).

## **Reproductive system**

Acute and chronic stress influences both male and female reproductive systems causing a disruption in the normal physiological processes as well as playing a role in causing various disorders.

- Sexual arousal: During stress, the levels of testosterone are dysregulated in males leading to a decreased libido or sexual drive. Furthermore, decreased sexual arousal in both males and females could occur secondary to stress-induced fatigue and depression (APA, 2018).
- Reproductive disorders: In males, reduced libido could lead to impotence and erectile dysfunction. Low sperm count and motility induced by stress lead to difficulty in conceiving and associated anxiety. Infections of the reproductive organs could be the result of a depressed immune system that is seen in chronic stress (APA, 2018).

In females, stress could induce changes in menstruation in terms of the regularity and length of the cycle and causing more painful menses (APA, 2018). Premenstrual syndrome (PMS) which includes symptoms such as fluid retention, bloating, abdominal cramps and mood swings (irritable and low mood) exacerbates during stress making it more difficult for women to cope with the same (APA). Disorders such as polycystic ovarian syndrome (PCOS) and infections namely herpes simplex virus could precipitate in women during stress (APA, 2018).

In addition, females experiencing increased stress during pregnancy are more likely to develop depression and anxiety during this time. This could further lead to a detrimental effect on the newborn (APA, 2018).

- Menopause: Females undergoing stress during menopause may experience an exacerbation of symptoms associated with this physiological process such as hot flashes, changes in mood such

as irritability and low mood and associated distress. This could act as a stressor itself further deteriorating the condition (APA, 2018).

## **STRESS DURING EXTREMES OF LIFE: INFANCY AND AGING**

An important domain of stress is time. Stress does not necessarily have the same implications on all individuals or in fact, on the same individual at different phases of life. How does stress affect the too little and the too old?

### *Stress in infancy:*

What seem striking is the studies that have been conducted on young rodents wherein it was observed that a period of decreased responsiveness to stress termed as the “Stress Hyporesponsive Period- SHRP” occurs in infancy coinciding with the post natal period necessary for development of the brain (Sapolsky & Meaney, 1986). Analogous to this, another study found a similar period of hyporesponse to stress in infants (Gunnar & Donzella, 2002). The SHRP corresponds to an absence of significant response (such as increased glucocorticoids/ epinephrine and their actions as described above) to stress seen in infants for an undetermined amount of time just after birth (Gunnar & Donzella, 2002). It was shown in various studies that when exposed to psychological stressors early in life (such as maltreatment, physical abuse, separation/neglect by parent) especially in a temperamentally vulnerable individual, a disruption in this SHRP occurs leading to earlier activation of the HPA axis, altered cortisol levels and subsequent maladjustment (Sapolsky & Meaney, 1986; Gunnar & Donzella, 2002).

### *Stress during aging:*

Stress and aging have a bidirectional relationship- each having its own effects on the other. With age, one seems reluctant to grow older and is preoccupied with the inevitable process of aging. This negative outlook on aging posing as stress is similar to the “stress is debilitating” mindset and has its own morbid effects on the mind and body. Similarly, coping with stress in old age is a challenge as the number of co-morbidities in such individuals itself is demanding to begin with. As already outlined in the chapter, a number of age-related co-morbidities such as coronary artery disease, chronic respiratory diseases and malignancy is related to stress.

Thus, stress and aging form an intricate relationship- one that is both complex and toxic eventually leading to adverse outcomes.

At the cellular level, ageing is associated with senescence of cells. The cause of this cellular senescence is multifactorial, of which DNA damage appears to play a central role. DNA damage is mediated through replicative as well as stress (genotoxic and/or oxidative) induced senescence (Grabowska et al., 2017). With increasing age, the ability to repair this DNA damage decreases and accumulation of toxic products such as free radicals result in cell senescence (Grabowska et al., 2017). Oxidative stress also leads to a variety of age-related disorders such as cancer, atherosclerosis and neurodegenerative diseases.

**Box 7: Fine dine & little wine may buy you some time!**

Increasing research has shown that flavonoids- a group of compounds found in natural foods such as vegetables, fruits, tea, cocoa and red wine- have anti-oxidant properties along with immune system benefits (Pietta, 2000). They may play a protective role against cancer.

Sirtuin is another compound found in red wine and dark chocolate amongst other foods. Sirtuins are indispensable for DNA repair, controlling inflammation and antioxidative defense which makes them good anti-senescence/anti-ageing targets (Grabowska et al., 2017).

## **STRESS THROUGH THE AGES- FOOD FOR THOUGHT**

Charles Darwin formulated the theory of biological evolution through natural selection wherein he stated that all organisms develop through the natural selection of small, inherited variations (heredity) which increases the ability of an individual to adapt and compete for survival. When we extrapolate this theory to the stressors affecting human adaptation and survival from the beginning of mankind, it is interesting to find that the same mechanisms that may have proven to be protective initially, now serve as an etiological factor for many disorders (Chrousos, 2004).

*Table 3* below shows the protective mechanisms used against stressors as well as the disorders that have arose by the same mechanisms during these contemporary times.

**Table 3. Genetics as a double-edged sword (Adapted from: Chrousos, 2004)**

Response to survival threat	Selective advantage	Contemporary disease
• Combat starvation	Energy conservation	Obesity
• Combat dehydration	Fluid & electrolyte conservation	Hypertension
• Combat infectious diseases	Potent immune reaction	Autoimmunity/Allergy
• Anticipate adversaries	Arousal/fear	Anxiety/insomnia
• Minimize exposure to danger	Withdrawal from danger	Depression
• Prevent tissue strain and injury	Retain tissue integrity and reserve	Pain and fatigue syndromes

## CONCLUSIONS

Stress is both- positive as well as negative depending on the intrinsic and extrinsic factors present in the stressful situation. While not every individual copes with stress in the same manner due to numerous variables, most effects of acute and chronic stress can ultimately be seen in all organisms in a stereotyped cascade of events leading to dyshomeostasis and other disorders. A number of physical and mental health disorders as well as physiological processes such as aging are associated with stress. Epigenetics, genetic mechanisms, environmental factors, temperament or mindset of an individual, diet and age- contribute to being a stressor while also playing a fundamental role in the response to stress. Finally, pathophysiology, effects and genetic role involved in stress and the mechanisms of adaptation that are understood today form just the tip of the iceberg. A variety of unknown physiological dysfunctions and disorders could have stress as the underlying core factor.

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## **STRESS AND COPING**

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### **OUTLINE**

- |                                 |                          |
|---------------------------------|--------------------------|
| 1. INTRODUCTION                 | 2. DEFINITION & HISTORY  |
| 3. THEORETICAL MODELS OF STRESS | 4. MEASUREMENT OF STRESS |
| 5. COPING                       | 6. CONCLUSIONS           |

## **INTRODUCTION**

The concept of Stress has remained relevant in psychology and mental health discourse over several decades. Stress refers to an experience of tension that subsumes physical, emotional and cognitive components. Eustress refers to positive stress which creates a healthy drive and enables people to achieve desired goals. Distress refers to negative stress which results in anger, frustration, sadness, anxiety and when goals are thwarted. While optimal level of stress is necessary for goal directed behaviour, severe acute stress or chronic stress can lead to a maladaptive response to an event or situation. In this chapter, we present an overview of the definition and history of stress, psychosocial theories, measurement and coping.

## **DEFINITION & HISTORY**

In the 19th century Claude Bernard posited that living things had an “internal environment” to which their behaviours can be attributed unlike nonliving things. He further expanded this notion by stating that in complex living organisms, functioning is dependent on both external and internal environment. Maintenance of life was noted to be dependent on the responses that kept the internal milieu constant (Goldstein & Kopin, 2007). Walter Cannon (1929) termed this process

as homeostasis. Though Bernard initially conceptualized the basis of current understanding of stress as challenges that can be detrimental to the integrity of an organism evokes responses to counteract those threats, the term stress was first used in this context by Cannon (Goldstein, 2010).

It was Hans Selye's work on stress which brought the concept into much attention. He is considered as the father of stress research. Selye (1976) defines stress as 'a state manifested by a syndrome which consists of all the non-specifically induced changes in a biologic system.' This full pattern was described as general adaptation syndrome (GAS). It involves three stages (a) alarm reaction, wherein at the onset of stressor organism initiates a series of responses, (b) resistance stage, where organism's initial response decelerates down and becomes adapted to the stressor and (c) If the stressor persists, resistance gives way to the stage of exhaustion. Long term effects of stress were explained through allostasis by Sterling and Eyer (1988). The conception of general adaptation syndrome was questioned by Mason pointing non-specificity of stimuli. He identified that all the stressful situations in experiments by Selye were novel, strange and unfamiliar. And thus animals experienced helplessness, uncertainty and lack of control. In situations lacking those characteristics general adaptation syndrome was not observed (Lyon, 2000).

## **THEORETICAL MODELS OF STRESS**

Different theoretical models explain the mechanisms of stress and its different manifestations. Systemic theory by Selye (GAS) popularized the concept of stress in the research field. It has been criticized for its generalistic approach and for its lack of sensitivity for response specificity and thus psychological theory of stress was put forth.

### **Transactional theory of stress**

Lazarus and Folkman's (1984) transactional theory views stress as a result of person's interpretation of the stressful stimuli and not merely by the presence of it (Zakowski et al., 2001). Since its first presentation the theory has undergone a series of revisions and the recent one explains stress as a relationship ('transaction') between individuals and their environment. Appraisal and coping seems to be two important concepts in the theory. When the person appraises a situation as demanding and perceives that his or her coping does not meet the demands stress

is expected to arise. The actual expectancies a person has about the significance and outcome of a specific encounter result in emotional responses including stress. Primary appraisal concerns whether the stressful situation poses a threat, harm or challenge to the person and secondary appraisal concerns about the coping resources he or she have. Coping is defined by Folkman and Lazarus (1980) as ‘the cognitive and behavioral efforts made to master, tolerate, or reduce external and internal demands and conflicts among them.’ They define problem focused and emotion focused coping as two different mechanisms of coping. Goh, Sawang, and Oei (2010) discussed the revised model of transactional theory of stress by suggesting the stress response can happen even at primary level of appraisal.

Lazarus (1993) believed that psychological stress theory and theory of emotion are almost indistinguishable and because there exists an overlap in two literatures, the two fields might be conjoined as the field of emotion theory. Since explanation of stress has also progressed from unidimensional to multidimensional it draws enough parallels with emotions and hence the range of understanding of its impacts has also broadened. In both psychological stress and emotions the achievement of ‘relational meaning’ through the process of appraisal seems quite significant. The emotional impact of a situation is determined not just based on the situation alone but the personal meanings (core relational theme) associated with it and the resultant emotion depends on the implication it has on the integrity of the person. Psychological stress theory also draws on the same lines. Lazarus considers molar (relational meaning) and molecular variables (personality and environmental) to explain the concept. Each emotion is expected to involve a different core relational theme. For instance, in the appraisal leading to anger the accountability of others is a vital component, while in pride, guilt, and shame self-accountability is essential. By influencing the person-environment relationship and its appraisal, coping moulds emotions. Coping involves attempts to change the way a problem/ situation is looked at or altering the emotions associated with it (emotion-focused coping), or attempts to change the person-environment realities behind negative emotions (problem-focused coping).

### **Sociological theories**

*Role Theory:* Role theory propounds that each individual plays different social roles which guides one’s actions and behaviors. When these roles become conflicting or one becomes overloaded with certain roles it ensues in stress. Research suggests that stress is high if one has to play a role involuntarily. Also if parents are highly

committed to the role and the role played is quite important parental strains are likely to occur (Carr & Umberson, 2013).

*Fundamental Cause Theory:* This theory stresses on the importance of social gradient of health. People on lower socioeconomic strata (SES) are exposed to a series of vulnerable situations and have stressors on physical, social, psychological and monetary domains. The life expectancies of higher and lower income groups vary by 7 years. SES is found to be inversely associated with coping resources, adaptive coping strategies and self-esteem (Hatzenbuehler, Phelan, & Link, 2013).

*Cumulative Disadvantage Theories:* Adversity begets adversity is the broad proposition of these theorists. People who have impoverished upbringing are expected to be at elevated risk for future stressors. Low SES in adulthood and the strains accompanied are thought to be the best predictors of poor physical and emotional health.

### **Socioeconomic Factors and Stress**

#### *(a) Poverty/unemployment*

Living with persistent poverty damages one's psychological health. Poverty brings along with it a lack of opportunity, reduced availability and accessibility to resources and a greater likelihood of experiencing difficult events. Literature demonstrates that low SES and income are associated with a range of psychopathology (Miech et al., 1999; Sapsolsky, 2004). Neighbourhood disadvantage is viewed as another causative dimension for psychological problems (Attar et al., 1994; Britt, 1994; McLoyd, 1998). Poor neighbourhood might result in fewer resources, less cohesiveness, and higher crime. The families tend to have high levels of conflict, harsher interaction and unresponsive parenting even leading to neglect (Repetti et al., 2002). Early exposure to such family environment might lead to physiological outcomes in children (HPA-axis activity) that are responsive for stress dysregulation (Evans & English, 2002; Repetti et al., 2002). Adolescents who experience poverty are more likely than their peers to engage in deviant behaviors with boys having externalizing disorder and girls expressing internalizing disorders. Schizophrenia was initially noted to be occurring largely in lower socio-economic groups. Drift hypothesis suggested that with the progression of illness an individual drifts down in the socio-economic strata. It was disproved later in further studies. Major depressive disorder occurred twice as high in low income group than in low income group (Lapouse et al., 1956).

*(b) Gender and Work*

To explore gender differences in the impact of stress on decision making, Lighthall et al. (2012) used functional magnetic resonance imaging (fMRI) to determine whether induced stress resulted in gender-specific patterns of brain activation during a decision making task. A gender-by-stress interaction was observed for the dorsal striatum and anterior insula. The findings demonstrated that the impact of stress on reward-related decision processing differs depending on gender in which males were shown to have faster processing and reward dependent behaviors during stress.

Chaplin et al., (2008) examined gender differences in emotional and alcohol craving responses to stress. Twenty seven adult men and women healthy adult social drinkers were exposed to individually developed stressful, alcohol-related, and neutral-relaxing imagery. Subjective emotions, behavioral/bodily responses, cardiovascular, and self-reported alcohol craving were assessed. For women sadness and anxiety was associated with stressful situations whereas in men alcohol cravings were reported.

From a series of studies of women and men, it was concluded that gender roles and psychological factors are more important than biological factors for the sex differences in stress responses (Lundberg, 2005).

In an attempt to understand influence of gender and culture on work stress of managers. Miller et al., (2000) collected data from male and female managers from four different countries on sources of occupational stress, coping and consequences of occupational stress. Significant differences were found only in the consequences of work stress for male and female managers.

A critical review by Gyllensten, and Palmer (2005) to investigate research on role of gender in workplace stress revealed inconsistent evidence. Bhui et al., (2012) reviewed 23 systematic review papers examining the interventions on psychosocial stressors in the workplace from 1990 to 2011. It included 499 primary studies; there were 11 meta-analyses and 12 narrative reviews. Meta-analytic studies and narrative reviews had consistent results. Individual interventions, cognitive-behavioral programme in particular, had greater effect size than organizational interventions on individual outcomes. Organizational interventions involving physical activity resulted in reducing absenteeism.

## MEASUREMENT OF STRESS

Stress and its implications are far reaching and it becomes important to have adequate and standardized measures to assess it. There exist a number of assessments including psychophysiological measures of stress and psychosocial measures of stress. An overview of self report and interview based assessments are discussed below:

### **Psychophysiological Measures:**

Typically, the effect of stress (psychological) is seen on objective parameters such as: changes in cortisol, heart rate, blood pressure, skin conductance and respiration. Physiological stress in manifests in altered sympathetic and parasympathetic nervous system activity.

### **Psychosocial Measures:**

#### *Daily event measures.*

The Daily Life Experiences Checklist (DLE; Stone & Neale, 1982) contains 78 events sorted into five domains—work, leisure, family, friends, financial, and other. Participants are asked to rate the events that happened since they “first awoke this morning.” Desirability and meaningfulness are also assessed for the rated events. A similar scale is the Daily Stress Scale that has 22 events and span for events that has happened in last 24 hours. Follow-up questions are also possible with this scale. There are scales that assess both desirable and undesirable events. Hassle Scale (DeLongis et al., 1988), a 53-item scale, includes both hassles and uplifts events. Inventory of Small Life Events (ISLE) which contains 178 items, of which 98 are positive and 80 negative (Zautra et al., 1986).

#### *Interval event/ Chronic event measures.*

Social Readjustment Rating Scale (SRRS) developed by Holmes and Rahe (1967) is one of the widely used measures to assess stress. Underlying premise of the scale is that there follows readjustment subsequent to a “life event” in one’s life. This is in line with Adolph Meyer’s notion of “life chart” to represent the relationship between psychosocial events and illness. The SRRS contains 43 items consisting of commonly experienced “life events” measured in terms of life change unit score (LCU). Subjects are asked to check if they have experienced any of the life events mentioned in the last 12 months. The total LCU score determines the risk of becoming ill within a specified time period.

To explore the presence of a traumatic event in one's life and also to assess its current impact on the person there are several scales available. Twenty item, Stressful Life Experiences Screening (SLES) and the Life Stressor Checklist—Revised (30 items) are examples of the same.

#### *Interview measures of major life events.*

Interview measures for assessing stress provide much richer data in terms of occurrence, nature, duration and its impact. Most researchers retain to scales because of the time consuming nature of interviews. The Life Events and Difficulties Schedule (LEDS, Brown & Harris, 1978), and the Standardized Event Rating System (SEPRATE, Dohrenwend et al., 1993) are the two major interview schedules in this area. The LEDS provides insight into details of each event, including the context in which the event occurred. It also dwells into the history of occurrence of similar impactful instances in the recent past. SEPRATE attempts to identify individual vulnerability through a series of forced questions which is followed by certain set number of structured questions. Desirability of the event, disturbances to daily life routines, threat to life etc. are some of the domains assessed.

## **COPING**

Stress evokes perceptions of threat, harm, and loss in multitude of ways. The way people chose to respond to these perceptions are termed “coping”. It can either be voluntary or involuntary. There exists variety of distinctions for coping:

*Problem versus emotion focus:* Problem-focused coping is directed at the stressor itself: taking steps to remove or to evade it, or to minimize its effect if it cannot be evaded.

*Emotion-focused coping* is aimed at diminishing distress triggered by stressors. Because there are various ways to reduce distress, emotion-focused coping includes a wide range of responses as noted by Carver and Smith (2010), ranging from self-soothing (e.g., relaxation, seeking emotional support), to expression of negative emotion (e.g., yelling, crying), to a continuous focus on negative thoughts (e.g., rumination), to attempts to escape stressful situations (e.g., avoidance, denial, wishful thinking).

*Engagement versus disengagement (approach versus avoidant):* As the name suggests engagement or approach coping is aimed at dealing with the stressor or related emotions, and disengagement or avoidance coping, is aimed at escaping the threat or related emotions (Carver & Smith, 2010).

Engagement coping is active and includes elements from both problem-focused coping and emotion-focused coping whereas disengagement coping is more passive and includes responses such as avoidance, denial, and wishful thinking. Disengagement coping involves an effort to act as though the stressor does not exist, so that it does not have to be reacted to, in any manner. This might not help in the long run as it does not deal with the stressor per se.

*Accommodative coping and meaning focused coping:* Accommodative coping entails attempts to adapt or adjust to the stressor either through problem focused or emotion focused coping methods. In ‘meaning-focused coping’ (Folkman, 2010) people draw on their beliefs and values to find, or remind themselves of, benefits in stressful experiences (Tennen & Affleck, 2002). It may include reorganizing priorities of life and adding positive colors to ordinary events in life.

*Proactive coping:* Some researchers (eg, Aspinwall & Taylor, 1997) believe that certain coping occurs proactively before the occurrence of any stressor. It differs from other methods of coping in that it is intended to prevent threatening or harmful situations from arising. Proactive coping is nearly always problem focused, involving accumulation of resources that will be useful if a threat arises and scanning for signs that a threat may be construing. It helps in being prepared for any adversities to occur, also minimize the impact of any such occurrences by knowing it in prior.

## **CONCLUSIONS**

Stress is very integral to human lives. Everyone experiences stress, both its positive aspects and negative aspects. We also cope with stress either in an adaptive or a maladaptive way. A comprehensive understanding of both biological and psychosocial aspects of stress and its measurement is critical to developing meaningful interventions.

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## **THE BIOLOGICAL MARKERS OF STRESS RESILIENCE**

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### **OUTLINE**

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|-------------------------------|---|
| <b>1. INTRODUCTION</b>        | <b>2. DEFINING RESILIENCE</b>               |
| <b>3. TYPES OF BIOMARKERS</b> | <b>4. CONCLUSIONS AND FUTURE DIRECTIONS</b> |

## **INTRODUCTION**

Stress-related disorders like anxiety and depression are among the most prevalent mental health disorders in the community. Stress exacerbates the morbidity of several physical conditions like cardiovascular and gastrointestinal disorders too. Stress as well as its consequences in an individual is also multidimensional (Rakesh *et al.*, 2019). The aftermath of a stressful event may disturb an individual's physical, mental, economic, or social resources. Such disturbances may induce a chronic lasting impact on their life (Cathomas *et al.*, 2019). However, there are inter and intra-individual differences in responding to similar stress. Stress response forms a spectrum between improved functional adaptability to extreme individual dysfunction (Rakesh *et al.*, 2019). Understanding the mechanisms underlying the different stress responses may shed light on novel concepts and therapeutic options (Walker *et al.*, 2017). Essentially, such information may reveal the way forward towards building adaptive/positive community mental health.

## DEFINING RESILIENCE

Resilience, an important determinant of positive mental health, may be static or dynamic but is a common phenomenon. The construct may enable the individual to remain unflustered through adverse events (static) or rapidly recover from the adversity related dysfunction (dynamic) (Kalisch *et al.*, 2015). The ability of the individual to maintain a stable level of functioning throughout events is referred to as Resilience (Bonanno, 2004). Resilience may represent the mechanisms of active adaptation in response to challenging events (Feder *et al.*, 2009). Definitions of resilience had evolved and continued to be redefined as scientific knowledge unwraps itself. Resilience is studied by various researchers from diverse disciplines, including psychology, psychiatry, sociology, corporate and more recently, biological disciplines, including genetics, epigenetics, endocrinology, and neuroscience (Feder *et al.*, 2009; Russo *et al.*, 2012). However, there is no consensus, on an operational definition exists, and also single well accepted instrument to define or qualify ‘resilience’ and quantify ‘resilience’ exist (Walker *et al.*, 2017). The ‘resilience’ concept has been researched even in the community, corporate/organisational world, to know the dynamic capability of an organization/community to successfully deal with significant change. However, in this chapter we are focusing the concept of resilience and biomarkers in an individual preventing the development of pathology.

Contextually, it is interesting to note that resilience has been conceptualized somewhat similar to Immunity (Cathomas *et al.*, 2019). Adequate natural and acquired immunity prevents infections and maintains a healthy body. Similarly, inherent and adaptive resilience may provide for disorder/dysfunction free healthy mind and body. Immunity is specific to each infectious agent. Are there resilient factors specific against individual psychiatric disorders? Or is resilience a unitary general phenomenon protective against different adversities? Stress inoculation models help in building resilience. Is this similar to vaccination provided immunity? Additionally, is resilience primarily “natural” or mostly adaptive/respondive? Generally, stress response leads to adaptive neuroplastic changes and alters the threshold of the individuals (McEwen & Stellar, 1993; McEwen, 2008). Such neuro-adaptations could essentially be conceptualised as acquired resilience. Again, is resilience either a health promotive agent? or a disease preventive agent? or an adaptive agent? Yerkes-Dodson law suggests that an individual’s performance/learning may increase based on the strength of stress/stimulus but only up to a point and may reduce on increasing the stress levels further (Teigen, 1994). So, what is this optimal stress point that favours learning and performance? How to identify

that point for a specific individual? Though many questions arise regarding stress vulnerability and protective resilience, the area is of immense research interest and a constantly evolving dynamic phenomenon (Osório *et al.*, 2016).

Exploring the markers/factors related to resilience may be as necessary as or relatively more important than the factors related to vulnerability. This may assist in understanding the pathophysiology of stress-related disorders better (Kalisch *et al.*, 2015). However, an individual's resilience is usually measured using subjective reports/questionnaires. Subjective reports are usually susceptible to bias and objective, reliable biological markers are indeed essential for the progress in the field (Osório *et al.*, 2016). With the advances in clinical research moving towards a trans-diagnostic approach (Insel *et al.*, 2010), it is imperative for resilience research also to adopt a trans-diagnostic approach (Kalisch *et al.*, 2015). Recent coronavirus infection pandemic has raised serious questions on ways to improve resilience in healthcare professionals. A Cochrane review did not find any positive findings, except fostering resilience training may reduce depression and stress symptoms in healthcare workers (Kunzler *et al.*, 2020). The common psychosocial resilience promoting factors are summarized in Table-1 (Feder *et al.*, 2009; Russo *et al.*, 2012; Osório *et al.*, 2016; Walker *et al.*, 2017). Better conceptualization of resilience may inform relevant mental health promotion, prevention, and clinical management strategies. Hence the focus of research in resilience is to inform the mental health promotion approach rather than the existing disorder-treatment model.

**Table-1: Psychosocial factors that promote resilience**

<b>Personal factors (core resilience)</b>	<b>Social and contextual factors (supportive resilience)</b>
Age	Social support
Gender	Social cohesion
Education	Early exposure to manageable stressors (stress inoculation)
Personality traits	Religion
Cognitive resources	Spirituality
Impulse control	Family support
Self-esteem, Optimism	Financial resources
Absence of mental illness (such as Schizophrenia, PTSD, Depression)	
Absences of chronic physical illness (such as Diabetes, Hypertension)	

## TYPES OF BIOMARKERS

Biomarkers are the cornerstone in understanding the differential response to similar stress across the population. Biomarkers are defined as an objectively measurable variable that reflects the specific underlying biological, pathological, or pharmacological process (Biomarkers-Definitions-Working-Group, 2001). The available biological markers of stress resilience are described below.

### 1. Neuroimaging markers

Increased grey matter volume in the right middle frontal and right superior frontal gyri is associated with competency and adversity in adolescents with a history of adversity (Burt *et al.*, 2016). In this large sample study, gray volume in the right prefrontal cortex was associated with high competence despite high adversity in adolescents (Burt *et al.*, 2016). The structural integrity of white matter tracts associated with cognitive and emotional control was positively associated with resilience in older adults with depression (Vlasova *et al.*, 2018). This was postulated as a biomarker for a better treatment response. Attenuated inter-hemispheric (left to right) sub-genual anterior cingulate cortex connectivity distinguished resilient recovered individuals from individuals with recurrent episodes of depression (Workman *et al.*, 2017).

In functional neuroimaging studies, maltreatment in childhood was associated with intra-limbic connectivity (between amygdala and hippocampus) whereas positive developmental adaptation was predicted by better fronto-limbic functional connectivity (Demers *et al.*, 2018). Among youths with a history of maltreatment, the ability to recruit prefrontal cortex control regions and thereby modulate amygdala reactivity during cognitive reappraisal tasks was associated with reduced risk of depression and anxiety (Rodman *et al.*, 2019). Attenuated reward response is a marker of the depressive trait. Healthy and resilient adolescents showed greater frontal cortical activation during reward anticipation (Fischer *et al.*, 2019). This reiterates the executive control of the prefrontal cortex and reflects positive adaptation (Buhle *et al.*, 2014; Demers *et al.*, 2018). Increased white matter connectivity within the right amygdala is associated with psychopathology following early-life adversity. Reduced right amygdala connectivity after childhood or early life maltreatment is shown to be a resilience marker (Lee *et al.*, 2012; Ohashi *et al.*, 2019). Effective prefrontal-amygdala connectivity is described as a protective mechanism against internalizing syndromes in adolescence (Herringa *et al.*, 2016).

## 2. Neurochemical markers

### *Monoamines:*

The crosstalk between the monoamines serotonin, norepinephrine and dopamine is postulated to underlie the synaptic plasticity changes in the limbic region during stress response (Arnsten & Li, 2005; Krystal & Neumeister, 2009). Norepinephrine projections from locus ceruleus to the amygdala, hippocampus, and prefrontal cortex are important in stress response (Southwick *et al.*, 1999). In animal models, it has been reported that norepinephrine transporter (NET) expression is reduced in locus ceruleus following chronic persistent stress and this leads to exaggerated availability of norepinephrine in the synaptic cleft of projection areas (Rusnák *et al.*, 2001). Lower levels of norepinephrine measured post-deployment in war veterans correlated with lower levels of PTSD symptoms. This marker may be used to prognosticate and differentially categorize at-risk individuals for further monitoring (Highland *et al.*, 2015). An increase in NET expression in the prefrontal cortex following chronic stress is hypothesized as a normal mechanism attempting to maintain dopamine and norepinephrine tone in this region (Miner *et al.*, 2006).

Serotonin is a key regulator of stress and anxiety. Reduced availability of serotonin (5-HT) at the amygdala and other limbic regions leads to the manifestation of stress-related mental health conditions (Wu *et al.*, 2013). Stimulation of 5-HT-2A and 5-HT-1A receptors lead to anxiogenic and anxiolytic effects respectively (Akimova *et al.*, 2009). The 5-HT-1B receptor is an autoreceptor that regulates the level of serotonin at the synaptic cleft through serotonin transporters. Following stress, the inability to down-regulate the 5-HT-1B activity is hypothesized to underlie the pathogenesis of psychiatric manifestations. Adequate down-regulation of the 5-HT-1B receptor leads to increased availability of serotonin at the synaptic cleft and ultimately, resilient stress response (Kilpatrick *et al.*, 2007; Krystal & Neumeister, 2009). Stress results in reduced release of dopamine in the nucleus accumbens and activates dopamine release in the prefrontal cortex. Decreased levels of dopamine in the prefrontal cortex are associated with poor executive control and persistence of fear response (Morrow *et al.*, 1999). However, the research on the role of dopamine in stress response is limited (Charney, 2004).

### *Neuropeptide-Y (NPY):*

NPY is one of the abundant brain polypeptides. Higher concentrations of NPY are found in locus ceruleus, hypothalamus, periaqueductal grey area, hippocampus, and amygdala. NPY-Y1 receptor is implicated in animal models of stress (Thorsell,

2008). NPY is usually released along with norepinephrine during sympathetic system activation. NPY is postulated to prevent the persistent activation of the sympathetic nervous system (Southwick *et al.*, 1999). Administration of NPY has led to reduced retention of stressful memories, improved extinction of fear-related startle, and anxiolytic effects in animal models (Gutman *et al.*, 2008). In human studies, higher NPY levels were associated with better adaptation and lesser dissociation following stressful events (Morgan III *et al.*, 2002). Interestingly, a higher NPY/ Corticotropin-releasing factor ratio correlated positively with better resilience (Lambert *et al.*, 2020). The potential utility of intranasal NPY to reduce anxiety symptoms is currently being evaluated (Sayed *et al.*, 2018).

#### *Corticotrophin Releasing Hormone (CRH) and Cortisol:*

CRH is an important mediator of the immediate stress response. Through the activation of adreno-cortico-tropic-hormone (ACTH) release and ultimately cortisol secretion from the adrenal cortex, CRH mediates the neurohumoral stress response (Feder *et al.*, 2009). Secreted cortisol has polymorphic effects on arousal, memory consolidation, and immune alterations. Persistent secretion and high levels of cortisol are toxic to neurological, metabolic, and immune systems (Gold *et al.*, 2002). Lower levels of CRH were reported in resilient individuals (Charney, 2004). In healthy adults, higher resilience was reported to be associated with higher urinary cortisol levels (Simeon *et al.*, 2007). However, resilience was not related to plasma cortisol and stress-related cortisol secretion (Simeon *et al.*, 2007). Hair cortisol may be a reliable measure compared to urinary or plasma cortisol (Gray *et al.*, 2018). A cross-sectional study suggested a possible association between hair cortisol levels and resilience measures (Garcia-Leon *et al.*, 2019). Nevertheless, the results are mixed and concepts like inverted U type cortisol levels are proposed to understand the neurohumoral stress response (Southwick *et al.*, 2003; Lambert *et al.*, 2020).

#### *Dehydroepiandrosterone (DHEA):*

DHEA is a neurosteroid and precursor of adrenal steroid synthesis (Lambert *et al.*, 2020). Similar to NPY's role in regulating the sympathetic nervous system, DHEA is postulated to play a crucial role in the regulation of cortisol secretion. Anti-oxidant and anti-inflammatory actions of DHEA are hypothesized to underlie its anxiolytic effects (Taylor, 2013). Studies on healthy military personnel had suggested that individuals with higher DHEA to cortisol ratio had performed better during acutely stressful situations and had lower dissociative symptoms

(Morgan *et al.*, 2004; Morgan III *et al.*, 2009). The positive effects of DHEA on emotional regulation, memory enhancement, and as an antidepressant agent are well known (Morgan III *et al.*, 2002; Sripada *et al.*, 2013). Recently, higher DHEA/Cortisol ratios are reported to be associated with higher resilience in animal models (Lambert *et al.*, 2020).

*Oxytocin:*

Oxytocin is a neuropeptide hormone well-known for regulating affiliative behaviours. Multiple studies suggest the importance of oxytocin in social interactions and cohesion (Insel, 2010). Given the important role of social support in adapting to stressful adversities, oxytocin related human ability to reduce fear and improve social interaction is an interesting avenue for resilience research (Walker *et al.*, 2017). Experimental animal studies suggested the role of oxytocin in promoting resilience against the effects of neonatal isolation (Barrett *et al.*, 2015). Observational human studies, however, reported an inconsistent association between oxytocin levels and PTSD manifestations (Walker *et al.*, 2017). Nevertheless, the oxytocin system appears to inform the potential interplay between social behaviours and resilience.

*Allopregnanolone:*

Allopregnanolone is a metabolite of progesterone. It is a Positive Allosteric Modulator (PAM) at the gamma-aminobutyric acid (GABA) receptor (Melcangi & Panzica, 2014). Enhancement of GABAergic tone is postulated to be the mechanism underlying the anxiolytic and anticonvulsive actions (Schüle *et al.*, 2014). Acute stress results in increased allopregnanolone levels that regulate the stress-induced HPA axis pathway. This regulation is the key to achieving homeostasis following stressful events (Schüle *et al.*, 2014). Chronic stress leads to the downregulation of allopregnanolone levels which may result in dysregulation of the HPA axis. In rodent models, administration of allopregnanolone during stressful paradigm prevented the anxiety and depressive behaviours (Evans *et al.*, 2012). Recently, Intravenous Brexanolone (allopregnanolone) infusion received Food and Drug Administration (FDA) approval for use in post-partum depression (Meltzer-Brody & Kanes, 2020).

*Brain-Derived Neurotropic Factor (BDNF):*

BDNF belongs to the neurotrophin growth factor family. BDNF plays a crucial role in regulating the growth and differentiation of neurons and neuronal plasticity in

different brain regions (Huang & Reichardt, 2001). Downregulation of hippocampal BDNF gene expression and circulating BDNF levels were associated with stress-related psychiatric disorders and suicidal behaviour (Duman & Monteggia, 2006; Duman & Aghajanian, 2012). Hippocampal BDNF expression is hypothesized to be a marker for stress resilience (Wu *et al.*, 2013).

### **3. Neurogenetic markers**

Genetic polymorphisms involving molecules related to the HPA axis (Sarapas *et al.*, 2011), monoamine transporters (Karg *et al.*, 2011), metabolic enzymes (Heinz & Smolka, 2006), and neuropeptides (Alexander *et al.*, 2010) confer increased vulnerability to developing stress-related disorders (Feder *et al.*, 2009; Russo *et al.*, 2012). Recently, circulating serum micro-RNA (miRNA) is identified as a potential biomarker to distinguish resilient individuals following trauma from PTSD patients (Snijders *et al.*, 2019). Epigenetic modifications (Dudley *et al.*, 2011) (like DNA methylation, histone acetylation, and methylation) secondary to environmental and social influences play an important role in the development of affect and behavioural regulation (Sun *et al.*, 2013).

### **4. Neurophysiological markers**

#### *Heart Rate Variability (HRV)*

HRV is the time interval variation between consecutive heartbeats. It is measured by the decomposition of RR intervals from an electrocardiogram (Perna *et al.*, 2020). HRV primarily suggests the cardiovascular adaptability to sudden changes in homeostasis. Considerable overlap exists between emotion regulation networks and cortico-subcortical regions that modulate the autonomic nervous system (Thayer *et al.*, 2012). A meta-analysis suggests a significant relationship between HRV and cerebral blood flow in the prefrontal cortex and amygdala (Thayer *et al.*, 2012). The parasympathetic vagal tone may play an important role in regulating the allostatic system, immune, cognitive functions, and better emotional regulation (Perna *et al.*, 2020). High-frequency band (HF) and Root Mean Square of Successive RR interval Differences (RMSSD) are potential biomarkers that suggest resilience (Perna *et al.*, 2020). HRV is identified as a promising tool in different clinical trials. Cardiac vagal tone related HRV measures are associated with better cognitive flexibility (Alacreu-Crespo & Costa, 2018), emotion regulation (Nasso *et al.*, 2019), neurohumoral(Pulopulos *et al.*, 2018), and neuroimmunological regulation (Woody *et al.*, 2017; Williams *et al.*, 2019). This indirectly reflects the inhibitory effects of the central parasympathetic tone on the HPA axis and inflammation

following stress. HRV may be postulated as a global index of adaptability and flexibility while facing stressful situations (Perna *et al.*, 2020). However, vagally mediated index of HRV may be more promising and easily applicable non-invasive biomarker.

#### *Gamma oscillations:*

Gamma frequency oscillations (30-200 Hz) including the high-frequency oscillations measured by electroencephalography (EEG) reflect the increased neuronal firing (Colgin *et al.*, 2009) 2009. Gamma rhythm facilitates improved coordination between hippocampal and cortical structures during cognitive tasks (Spellman *et al.*, 2015). The power (amplitude) of gamma rhythm during rest and cognitive tasks are reportedly different between healthy controls and depressed patients (Siegle *et al.*, 2010). Administration of intravenous ketamine, an antidepressant agent is reported to increase gamma power in depressed individuals and hence is considered as a possible mechanism underlying its rapid action (Hakami *et al.*, 2009). Results from animal models suggest that increased gamma coherence may be a potential biomarker in stress resilience research (Fitzgerald & Watson, 2018; Thériault *et al.*, 2019).

## **5. Immune markers**

Stress usually results in increased circulating pro-inflammatory cytokines like interleukin – 6 (IL-6) and interleukin-1 $\beta$  (IL-1 $\beta$ ) (Steptoe *et al.*, 2007). IL-6 and IL-1 $\beta$  are conceptualized as potential biomarkers of PTSD illness severity and duration respectively (Walker *et al.*, 2017). In animal models, resilient mice had shown relatively lower levels of IL-6 than the susceptible ones (Hodes *et al.*, 2014). Lower stress-induced cytokine reactivity correlated with lower levels of psychopathology later (Hodes *et al.*, 2014). In healthy young females, following laboratory stress experiments, lower salivary proinflammatory cytokines were related to better cognitive control (Shields *et al.*, 2016). Chronic unpredictable stress and depression are associated with microglial activation and increased Blood-Brain Barrier (BBB) permeability. Leaky BBB results in the infiltration of inflammatory cytokines that may adversely affect neuronal function (Kreisel *et al.*, 2014). Hence, lower levels of pro-inflammatory cytokines following stressful situations may be a potential indicator of stress resilience (Menard *et al.*, 2017). A well conducted study in war veterans demonstrated that PTSD severity is associated, specifically, with four dysregulated chemokines (CCL13, CCL23, CCL25, and CXCL11). CX3CL1 (fractalkine) is a large chemokine protein may predict resilience (Zhang *et al.*, 2020).

## 6. Neurocognitive markers

A recently proposed framework suggests the role of “appraisal” as a common mechanism that mediates the evaluation of a stressful event, self-efficacy, and probable outcomes. Negative appraisal about the magnitude and probability of the event and doubts about self-efficacy in handling the stress may lead to dysfunction (Kalisch *et al.*, 2015). Appraisal of the event is conceptualized as a common cognitive mechanism of stress response rather than as a resilience factor. Despite its theoretical framework, this approach does not provide measurable biological markers and indicators. The critics of the positive appraisal mechanism report it to be short-lasting and unsuitable for enduring persisting stressors (Beer & Flagan, 2015).

### Highlights

- Psychological resilience refers to the individual’s ability to face, withstand, and positively adapt to adverse events.
- Progress in resilience research is hampered by the subjective nature of the psychometric instruments currently used.
- Objective standardized biological markers of stress resilience are searched with avid interest recently.
- A summary of neuroimaging, neurochemical, physiological, and immune markers of resilience is presented in this chapter.

## CONCLUSION AND FUTURE DIRECTIONS

Stressful events lead to a coordinated response from multiple systems and ultimately results in increased energy consumption. Resilience too may increase energy consumption similar to or relatively more than stress-induced changes. Conversely, resilience may as such represent the mechanisms that reduce such energy consumption and oxidative stress ultimately inducing a protective effect. Comprehensively defining the concept, objectively measuring the resilience through the identification of biomarkers and targeted interventions to enhance resilience may play a crucial role in health promotion in the near future. An integrated framework assessing vulnerability and resilience biomarkers may better guide the progression, prognosis, and clinical decision making for individual psychiatric illnesses. The therapeutic implications of resilience biomarker identification are huge and may pave way for innovative molecular drug targets for stress-related disorders.

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## **STRESS & ACCELERATED AGING**

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### **OUTLINE**

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## **INTRODUCTION**

Aging is a complex intraindividual process, defined as a time-dependent progressive loss of the individual's physiological integrity, which eventually leads to deteriorated physical function (López-Otín et al., 2013). Essentially this refers to a whole-body deterioration. What must draw our attention to aging in the context of stress is that, aging is negatively associated with the ability to respond to stress. In contrast, it is positively related to the homeostatic balance. To put it simply, the incidence of pathology (physical/mental) and death remains the final consequence of aging (Kowald and Kirkwood, 1996). That being said, can stress, in turn, lead to aging? In this chapter, we shall highlight how the impact of psychological stress on the aging process may vary within different individuals based on the differences in sensitivity defined by a variety of factors. coping strategies, disposition, temperament, and cognitive attributional styles.

Aging is essentially a reflection of cellular and molecular damage that an individual accumulates over his lifespan. There is no one theory that comprehensively explains the underpinnings of aging. It is in fact, linked to several mechanisms as shall be discussed in this chapter. In all of this, a term of greater interest would be that of accelerated aging, a process that occurs earlier in life than in natural course. A key question that can be raised in this regard would be: are there biological processes that set apart mechanisms of normal cellular aging from that of accelerated aging. In other words, it is important to understand if cellular aging is representative of a simple increase in the pace of the processes that govern aging, or is it a distinct pathological aging process of its own?

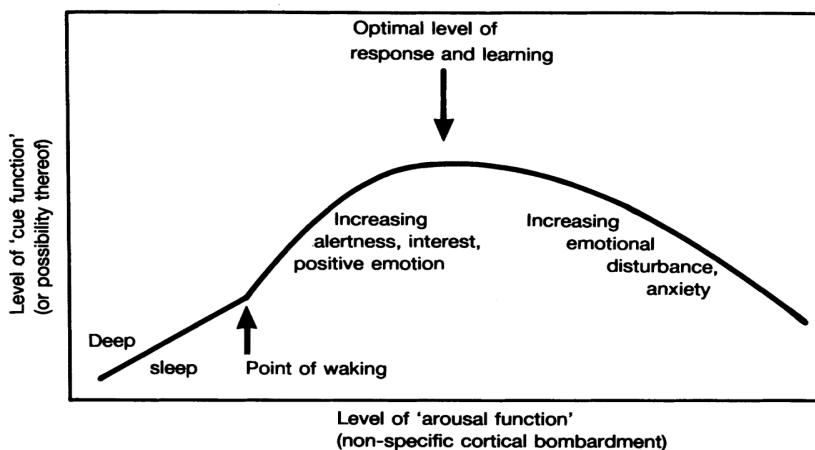
## **STRESS**

Selye (1965) coined the term stress and defined it as “the non-specific responses of the body to any demand for change”(Selye, 1965). It refers to the involvement of the body’s Autonomic Nervous System (ANS), comprising of sympathetic Nervous System (SNS) and Parasympathetic Nervous System (PNS), which in turn, regulate heart rate, respiratory rate, blood vessel, galvanic skin response, etc. Stressful situations trigger SNS that facilitates “fight or flight” response. In contrast to this, activity in PNS increases during any restful event.

### **Eustress vs Distress**

Stress may be viewed as being of 2 forms. It was Selye who introduced the concept of positive stress, namely eustress (Selye, 1974). Eustress is “healthy, positive, constructive results of stressful events and stress response” (Kupriyanov et al., 2014). Essentially the adaptiveness (nature of response) towards stress helps distinguish eustress and distress. Lazarus considers eustress as a positive cognitive response to a stressor, which associated with positive feelings and a healthy physical state (Lazarus, 1993). Another way of understanding eustress was developed on the Yerkes-Dodson Law (1908) that was later modified by Hebb(D.O. Hebb, 1955). It was suggested that low-to-moderate doses of stress is beneficial to performance until some optimal level is reached, after which performance will decline. This is recognised as the inverted U relationship as shown in figure 1.

Figure 1. The relationship between arousal function and cue function, according to Hebb, adapted from Hebb, 1955, p.250)(D.O. Hebb, 1955)



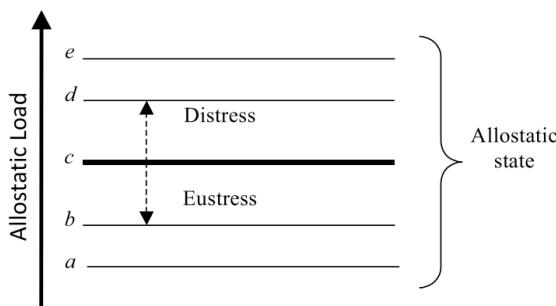
### Theory of Homeostasis and Allostasis

Homeostasis includes those aspects of physiology (pH, oxygen tension, body temperature for homeotherms) that help maintain life. Allostasis refers to those aspects of physiology that help us adapt. In other words, it is an active process of maintaining/re-establishing homeostasis in the face of environmental-life events/stress. Once the stimulus has disappeared, an organism tries to return to its original state. It may be either successful in restoring balance at the original level or it may restore balance at another level, causing a new stable state. This new level is called the “allostatic state”(Becker and Koob, 2016). The price the body pays for being forced to adapt to unfavourable psychosocial or physical situations is referred to as “allostatic load”. Physiologically, it signals either the presence of excessively strong stress (distress) or an ineffective reaction of the hormonal system to the stressor (McEwen, 2000). When a stressor overwhelms an organism, it may lead to allostatic overload resulting in a pathophysiological condition.

To illustrate the same in animals, note that the fat deposition in a bear preparing for the winter, a bird preparing to migrate or a fish preparing to spawn are examples of animals experiencing an allostatic load. Within limits, they are adaptive responses to seasonal and other demands. However, this is superimposed by additional load of unpredictable events in the environment, disease, human disturbance (for animals

in the wild), and social interactions, then allostatic load can increase dramatically and become allostatic overload leading to disease(McEwen, 2016).

Figure 2. Different states of allostasis. Adapted from Kupriyanov et al., 2014



In the above figure (figure 2), a, b and c represent states of allostasis that may be seen in eustress while d and e represent distress development (Kupriyanov et al., 2014).

### Differential Sensitivity to Stress

All individuals do not respond identically to similar stress. This inter-individual variation referred to as Differential Sensitivity (DS) is attributed to varying childhood temperaments and behavioural predispositions, to differences in brain structure and function, to the functional properties of neural circuitry and synaptic biology, and allelic and epigenetic variation within the human genome(Boyce, 2016). These parameters with special emphasis in children include:

- Stressors and adversities, including paternal depression (Cummings et al., 2007), marital conflict (El-Sheikh, 2005; El-Sheikh, Keller & Erath, 2007; Obradović, Bush and Boyce, 2011), parental psychopathology (Shannon et al, 2007), and overall family distress (Obradović et al., 2010);
- Positive environmental features, including parental warmth (Ellis et al., 1999), beneficial experiences and exposures (Pluess and Belsky, 2013), and supportive interventions (Bakermans-Kranenburg et al., 2008); and
- Inherent biological parameters, including physiological reactivity (Boyce et al., 1995; Alkon et al., 2006), differences in brain circuitry (Whittle et al., 2011), and gene polymorphisms (Bakermans-Kranenburg and Van IJzendoorn, 2006; Knafo, Israel and Ebstein, 2011; Manuck and McCaffery, 2014)aggressive.

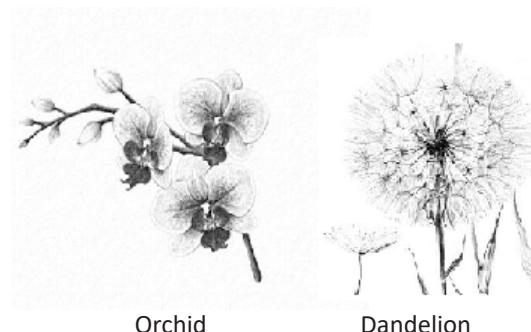
The relation of early adversity experiences to physiological sensitivity to stressors has been characterized as a U-shaped curve. It has been noted that children reared in both exceptionally high- and low-adversity contexts had the highest levels of autonomic and adrenocortical reactivity (Shakiba et al., 2020). This is to suggest that fostering vigilance to threat in conditions of adversity and by more effectively garnering nurturance and support within conditions of abundance and peace is promoted as it enhances the highest chances for survival.

#### *Threat sensitivity – Orchid or Dandelion?*

In experimental terms, a stressor is referred to as threat. The impact of a stressor on physical and physiological health depends on the appraisal (importance) given to the stressor or threat by the individual. Threat appraisals of an acute stressor is a reflection of two factors – dispositional threat sensitivity and the acute state responses to the specific tasks at hand.

Coping strategies, disposition, temperament, and cognitive attributional styles among others are collectively responsible for why different individuals respond differently to stress. (Folkman and et al, 1986; Denson, Spanovic and Miller, 2009; O'Donovan et al., 2009). The dispositional threat sensitivity component is relatively stable and is partly attributed to genetic factors of threat-related information processing, such as the serotonin transporter gene (Munafò et al., 2008). Threat sensitivity is also likely to be shaped by life experiences (eg., childhood adversity, post-traumatic stress disorder) through epigenetic modifications, changes in brain structure and function generated through neural plasticity, and shaping of cognitive-behavioural reactions (Boyce, 2016).

*Figure 3: Orchid Vs Dandelion*



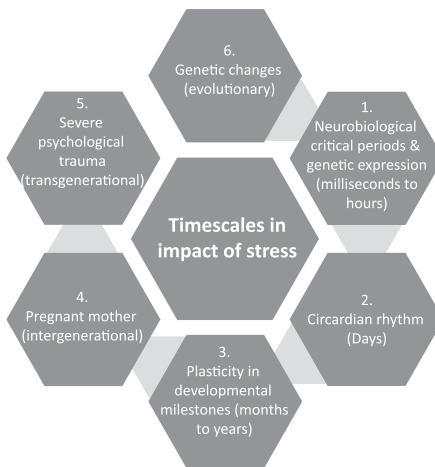
Orchids are more susceptible to surroundings whereas dandelions can thrive in even harsh weather conditions. Taking the flowers as an analogy, Boyce et al. stratified children into 2 subsets based on their responses to environment; orchid children as those who are highly sensitive with negative emotionality and dandelion children as those who are robust and resilient(Boyce, 2020).

Taking environment and threat sensitivity together, highly reactive individuals may show either exceptional vulnerability or exceptional resilience, depending on the level of stress and adversity that characterizes the ambient social environment (Ellis & Boyce, 2008).

### **The Role of 'Time' in Exposure to Stress**

An important and often overlooked aspect in the exposure to stress is trajectories of change that is induced by stress at different levels and the time it takes to impact various systems within an individual. This is complex as has been highlighted in figure 4. For eg., at a neurobiological (minutes to milli- seconds), genomic (hours to minutes), developmental (years and months), and evolutionary (centuries and millennia) time (Boyce, Sokolowski and Robinson, 2020).

1. At the cellular level, the opening and closing of critical periods in brain plasticity act at the millisecond to second time scale wherein the perineuronal net [PNN] which is the protective apparatus surrounding the parvalbumin – positive interneurons innervating pyramidal neurons is impacted. Similarly, genetic expression works at a time scale of few minutes to hours from the time of exposure to stress.
2. Circadian clock genes that generate circadian rhythms involved in many biological processes, including critical periods, sleep, metabolism, mood, and memory are impacted within a few days of stress exposure.
3. Critical periods in brain plasticity development are found within and across sensory, language, and higher cognitive domains reflecting in expression of developmental milestones.
4. Biological embedding of maternal stress in the developing foetus occurs in pregnant mothers.
5. Transgenerational inheritance of trauma in grandchildren. (E.g., holocaust survivors).
6. From an evolutionary time scale perspective, the genome is a repository of changes in DNA sequence.

**Figure 4: Timescales in the impact of stress**

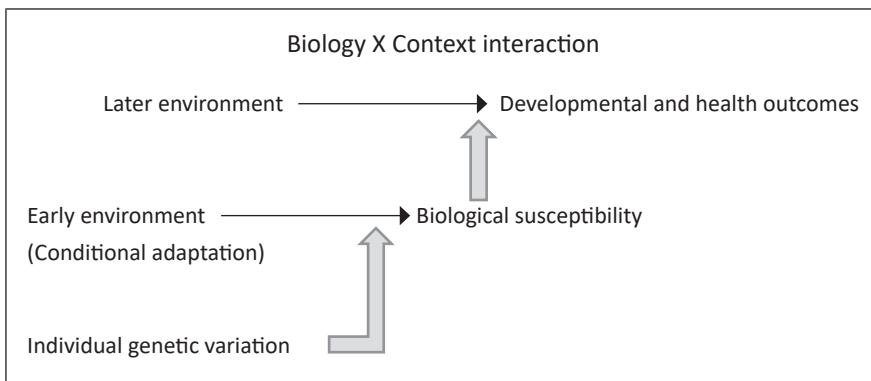
Another important perspective regarding time would be the time in the developmental trajectory of an individual when he/she is exposed to stress and the psychological outcomes that follow. There are some interesting findings in this regard. A study by Dunn et al. revealed that individuals first exposed to child maltreatment during early childhood had depression and posttraumatic stress disorder symptoms with twice the severity compared to those exposed during later developmental stages (Dunn et al., 2017) the impact of the developmental timing of exposure remains unclear. This study examined the effect of age at first trauma exposure on levels of adult depressive and posttraumatic stress disorder (PTSD).

Does this variability of time of exposure to stress determine the nature of psychopathology that may develop? In a sample of girls from the National Comorbidity Survey Replication-Adolescent Supplement, trauma during puberty conferred higher risk for diagnoses of anxiety disorders, while prepubertal trauma was significantly associated with diagnoses of depressive disorders (Marshall, 2016).

Differential susceptibility model: early environments and individual genetic variation determine biological susceptibility as a part of early conditional adaptation. Environments that the individual is later exposed to and biological susceptibility dictate developmental and health outcomes as a result of biology ×

context interactions as shown in figure 5. Such interactions and their triadic linkages to intermediate- and longer- term outcomes (Boyce, 2016).

Figure 5: Differential susceptibility model



## SCIENCE OF AGING

Research in this field has progressed towards delineating the hallmarks of aging (Tosato et al., 2007; López-Otín et al., 2013). These primarily include: (i). Cellular senescence (ii). telomere attrition (iii). mitochondrial dysfunction (iv). epigenetic alterations (v). genomic instability (vi). loss of proteostasis (vii). deregulated nutrient sensing (viii). stem cell exhaustion (ix). altered intercellular communication.

In the following section, an attempt has been made to carefully highlight the mechanisms that have clear evidence with respect to accelerated aging.

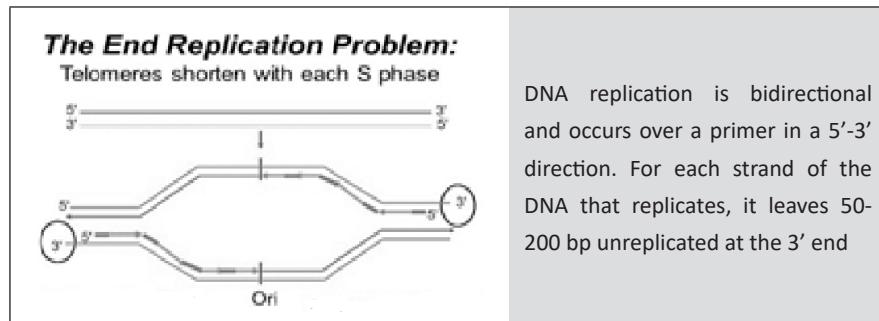
## CELL SENESCENCE

Hayflick, in 1984, through his experiments stated that normal cultured human foetal cells undergo a specific number of doublings. These cells can ‘remember’ how many times they have divided(Ruben and Biology, 2000). The molecular event counter or the “replicometer” was eventually traced to the nucleus - the telomere.

End replication problem and Hayflick limit: The properties of DNA replication prevent the cells from fully copying the ends of linear DNA, called telomeres. Because of the nature of lagging-strand synthesis, DNA polymerase cannot completely replicate the 3' end of linear duplex DNA. This was referred to as the end replication problem (FIG. 6). This repeated shortening of the DNA molecule at

each round of DNA replication might explain Hayflick limit wherein the cell is no more capable of dividing.

Figure 6: End replication problem



**Telomere and attrition:** Telomeres are G rich repeat sequences (TTAGGG) of 150-200 bps found at the chromosomal ends. Their function was initially not known. We now know that telomeres need to be long enough to form a T-loop structure in order to function as end “cap” for genome stability. Only when properly structured this way can telomeres prevent chromosomes’ ends from being wrongly identified as breaks in the double-strand (Boccardi and Boccardi, 2019). It was noted that as cells divided, telomeres shortened, which in turn, limited future cell proliferation. *In vivo*, this translates to disease and death. A ribonucleoprotein enzyme, telomerase, synthesises and elongates telomeres during and is thereby related to maximising cellular lifespan by more than five- fold! During acute stress, telomerase is more activated whereas in chronic stress it has lower activity (Telomerase Paradox).

$$\begin{aligned} \text{Telomere shortening} &= \text{cell senescence} \\ \text{Telomerase expression} &= \text{cell immortality} \end{aligned}$$

Telomeres are regions that are very difficult to replicate. New evidence is emerging that cell senescence may be occurring despite of telomeres being long and not critically short, as expected. Dysfunctional telomeres lead to premature cellular senescence irrespective of attrition length. Thus, it is necessary to analyse the state of each telomere in every single cell and not just to measure the total telomere lengths (TLs) on average (Boccardi et al., 2020).

What does this mean in the context of psychological stress?

Telomere shortening is considered the primary hallmark of aging. There exists a well-known relationship between stress and mental disorders. For e.g., in major depressive disease tend shorter telomere length has been noted (Damjanovic et al., 2007), especially in cases of longer duration and greater severity (Choi et al., 2008). There now appears to be a possible link between stress, mental disorders and telomere shortening as well.

Research evidence is in support of psychological stress being associated with short telomere length (Kiecolt-Glaser et al., 2011; O'Donovan et al., 2011a; Tyrka et al., 2009). In other words, psychological stress (allostatic load) translates to oxidative stress which is related to accelerated telomere shortening in humans (Epel et al., 2004). According to O'Donovan et al., psychological stress promotes exaggerated appraisals in vulnerable individuals which can possibly drive telomere shortening (O'Donovan et al., 2012). Conklin et al., suggest that psychosocial factors (including acute and chronic psychological stress, maternal stress, childhood maltreatment, trauma, or major depressive disorders) are associated with accelerated telomere attrition during life (Conklin et al., 2019).

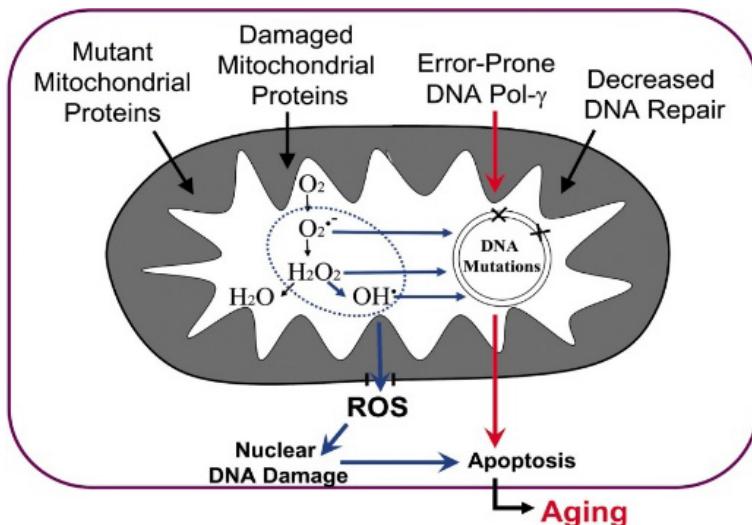
## **MITOCHONDRIA, REACTIVE OXYGEN SPECIES SYSTEM AND MACROPHAGES**

The respiratory chain and the oxido-reductases in the mitochondria organelle are a source of reactive oxygen species (ROS). There are several protective mechanisms against the production of ROS. Decrease in the potential of the mitochondrial inner membrane, decrease in the oxygen concentration by uncoupling and a slowdown of electron transport reduces the production of ROS while the presence of enzymes like Glutathione S transferase and thioredoxin reductase cause ROS inactivation.

Mitochondria can be affected by an increase in ROS concentration. It inhibits mitophagy (autophagy of mitochondria) or the mitochondrial fission process (breakup of mitochondrial tubules), which often precedes mitophagy. These mitochondria become a permanent source of ROS over time, and the cell acquires a new status of being senescence-associated secretory phenotype (SASP) (Coppé et al., 2010). This usually causes cell cycle arrest and stimulate immune responses. ROS also causes mitochondrial DNA (mt DNA) mutations. All of this adds up to accelerated aging.

At some point, the mitochondria may undergo mitophagy but in an incomplete manner. Such organelles then become the target of the innate immune system. This would translate into a perpetuating event with macrophages attaching the mitochondria due to it being a permanent source of pro-inflammatory factors. This phenomenon has been attributed to the causation of neurodegenerative processes, atherosclerosis and osteoporosis.

**Figure 7: ROS, mitochondria and aging (Adopted from Loeb, Wallace and Martin, 2005)**



*What does this mean in the context of psychological stress?*

Mitochondrial allostatic load (MAL): The mitochondria can suffer dysregulation resulting from structural and functional changes that occur in it in response to stressors. Psychological stressors include adverse childhood experiences (ACE), discrimination, job strain, low socioeconomic status, emotional states, psychopathology, social isolation and caregiving, among others. The primary challenges that overwhelm its capacity to respond include the demand for ATP and other biomolecules for maintaining cell function and survival, as well as providing biochemical signals (e.g., limited amount of ROS). This can ultimately lead to impaired cell function, senescence, and cell death.

Thus, systemic allostatic load can cause mitochondrial allostatic load which in turn perpetuates the systemic allostatic load and overload. MAL is possibly linked to telomere dysfunction and other mechanisms in causing accelerated aging and senescence. Other significant aetiopathogenesis in MAL promoting accelerated aging include release of chromatin-remodelling signals and thus altered gene expression, and mtDNA damage leading to compensatory increase in mtDNA copy number(Picard and McEwen, 2018).

## **PROINFLAMMATORY PHENOTYPE OF IMMUNE CELLS**

### **Inflammaging**

The increase in pro-inflammatory markers in addition to alterations in innate immune responses is labelled as “inflammaging”. Pro-inflammatory cytokines primarily include interleukin-1 (IL-1), IL-6 and tumour necrosis factor alpha (TNF- $\alpha$ ). These are increased by SASP (senescence associated secretory phenotype). Inflammaging is seen as a consequence of an aging immune system or immunosenescence, which implies the inappropriate response of adaptive immunity to pathogens exposure and other types of chronic stress in aging individuals (Olivieri et al., 2015; Goronzy & Weyand, 2017).

## **PSYCHIATRIC DISEASE BASED OXIDATIVE STRESS**

### **INDICATORS**

We have now come to a clear understanding of the impact of psychological stress in inducing oxidative stress at a cellular level and its detrimental effects on cell functioning, aging, disease causation and death. Hassan et al., has attempted to highlight an exhaustive list of oxidative stress related biochemical markers in the context of psychiatric illnesses. Reactive oxygen and nitrogen species cause highest cellular devastation. A few of these parameters have been listed in Table 1 (Hassan et al., 2016)

**Table 1: Oxidative stress related biochemical markers in the context of psychiatric illnesses**

	Name of the disorder	Key biochemical parameter	Reference
1.	Alcohol abuse	Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma Glutamyl- transferase (Gamma-GT), and Levels of Cholesterol, Triglyceride (TG), and Uric Acid Serum Malondialdehyde (MDA) Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPX) Activities CAT	(Miller, 1999)
2.	Attention deficit disorder	Malondialdehyde (MDA), paraoxonase and arylesterase enzyme activities	(Bulut et al., 2013)
3.	Bipolar disorder	Thioredoxin (TRX)	(Genc et al., 2015)
4.	Hypochondriasis	Ascorbic acid	(Diliberto et al., 1991)
5.	Insomnia	Glutathione Peroxidase (GSH- Px), Superoxide Dismutase (SOD), and Myeloperoxidase (MPO) Activities and Levels of Reduced Glutathione (GSH) and Malondialdehyde (MDA)	(Gulec et al., 2012)
6.	Manic episode	Thiobarbituric Acid Reactive substances (TBARS), Superoxide Dismutase (SOD), Catalase (CAT), and Neuron-Specific Enolase (NSE)	(Machado-Vieira et al., 2007)
7.	Psychotic disorder	Metabolomic Profiling	(Fournier et al., 2014)
8.	Trichotillomania	N-Acetylcysteine (NAC), Oxidative Stress Levels	(Mudla, 2013)

## CONCLUSIONS

The biological systems that influence accelerating aging and serve as the link between stress and accelerated aging has been highlighted in this chapter. The reliability of the findings is due to the evidence furnished in the multitude of similar work done by researchers in this growing field. It is yet to be understood fully if all the hallmarks of natural aging are pressed into effect in accelerated aging as well. Other interesting aspects that await clarification is the influence of chronological age on accelerated cellular aging in the context of psychological stress.

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## Part II

# STRESS RELATED DISORDERS



*Part II of the book focuses on stress related medical disorders. For the sake of clarity in this book, medical conditions are classified as physical and psychiatric disorders. This part discusses the various role of stress on various physical diseases ranging from the respiratory, endocrine, cardiovascular, and nervous systems. Psychiatric disorders in which stress is implicated as the etiological agent, such as acute stress disorder, adjustment disorder, and post-traumatic stress disorder, are discussed in length about the role of stress in these psychiatric disorders and various management pharmacological and non-pharmacological strategies. Stress-related and stress-induced psychotic disorders cover the role of stress among affective and non-affective psychotic disorders. Acute and transient stress psychotic disorders are also discussed with the role of stress in evolving as illness. At the end of this part, readers shall understand the closer role of stress among stress related medical (psychiatric and physical) disorders.*

<b>7</b>	<b>Stress and Physical Disorders</b> <i>Barikar C Malathesh, Anil Kumar Mysore Nagaraj, Vinutha Ravishankar, Prabhat Kumar Kodancha, Channaveerachari Naveen Kumar</i>
<b>8</b>	<b>Stress Related and Stress Induced Psychosis</b> <i>Prateek Varshney, Santosh Kumar Chaturvedi</i>
<b>9</b>	<b>Stress and Adjustment Disorder</b> <i>Guru S Gowda, Barikar C Malathesh, Narayana Manjunatha</i>
<b>10</b>	<b>Stress and Acute Stress Disorder</b> <i>Shalini S Naik, Barikar C Malathesh, Narayana Manjunatha</i>
<b>11</b>	<b>Stress and Post-traumatic Stress Disorder</b> <i>Nilamadhab Kar</i>

## **STRESS AND PHYSICAL DISORDERS**

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### **OUTLINE**

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| 7. STRESS AND IMMUNE SYSTEM           | 8. STRESS AND ENDOCRINOLOGY               |
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## **INTRODUCTION**

Stress is the body's reaction to a change that requires a physical, mental or emotional adjustment or response. The word 'stress' was coined by an endocrinologist Dr Hans Selye in the year 1936. He defined stress as 'the non-specific response of the body to any demand'. Stress may be broadly classified as 'Eustress' if it motivates a constructive behaviour and 'Distress' if it triggers a disease.

Stress is implicated as one of the factors in increased morbidity and mortality associated with common physical illnesses. Both physiological and psychological stress has been shown to increase the odds for the onset and progression of chronic diseases. The link between stress related variables and physical health related outcomes have been an area of interest to physicians, physiologists, people working in neuroscience and psychology.

In this chapter we shall limit ourselves to the stress being the **Psychological stress** and its impact on **Physical health**. The attempt in this chapter is to present current understanding of impact of psychological stress on the different organ systems of the body; and the benefits on physical health of reduction or controlling of psychological stress. The overall impact of physical illnesses on the quality of life has been summarized in the management section of the chapter, though we have not covered the detailed intricacies of the same. We have tried to provide a holistic approach to stress management for use by various clinicians in their routine clinical practice. The understanding here in this area is undergoing different levels of evolutions for different disorders which might result in the apparent disorganization in the holistic understanding of the interaction of psychological stress on the body.

## **STRESS AND CARDIOVASCULAR HEALTH**

The association of psychological stress and cardiovascular health is the most researched area among all medical illnesses. The damaging effects of stress hormones (catecholamines, including epinephrine) on heart when it is exposed to higher levels of stress hormones for longer duration is fairly well established. The causal role of stress in increasing oxygen demand on the body, causing spasm of the coronary (heart) blood vessels, and causing electrical instability in the heart's conduction system are also reported thereby leading to cardiac catastrophes. (Crestani, 2016; Fioranelli et al., 2018).. The role of depression and mental stress, including the stress at work place have been established as important causative factors for coronary heart disease and hypertension (Khayyam-Nekouei et al., 2013). Possible factors leading to development of coronary heart disease and hypertension include personality traits, hypothalamic-pituitary activation, higher sympathetic activity(Cuevas et al., 2017), reduced parasympathetic tone , reduced heart rate variability, endothelial dysfunction, increased platelet reactivity and endothelial inflammation leading to athero-thrombogenesis. (Fioranelli et al., 2018).

Major depression is present in at least 30 – 40% of the cardiac patients and it predicts higher mortality. (Huffman et al., 2013). Extensive discussion on depressive syndrome and cardiac disorders is beyond the scope of this chapter. What is to be known is that there is overlap of presence of psychological stress in depression and cardiac disorders, the difficulty in delineation of coping behaviours to psychological stress and depressive symptoms and a wide meaning of “stress” associated in this field of study. Mental stress induced myocardial ischemia (MSIMI) is reported to be more common than exercise induced myocardial ischemia. Especially, women, unmarried men and those living alone seem to be at higher risk of MSIMI(Jiang et al., 2013). In patients with established coronary heart disease (CHD), mental stress induced myocardial ischemia (MSIMI) seems to be significantly higher in patients with depressive symptoms than patients without the same (Boyle et al., 2013).

The association of chronic stress and increased mortality due to cardiac issues in persons with type A and type D behavioural patterns has also been noted (Martin et al., 2011). It reflects the effect of chronic stress on increase in the heart rate, cardiac work and blood pressure, which in turn can result in myocardial infarction (heart attack), heart failure, abnormal heart rhythms, and stroke.

Stress as a causative factor of hypertension had been well accepted by the society in general much before the scientific community gathered evidence. The celebrated study of cloistered nuns in Umbria (Timio et al., 1988) who lived in a secluded and unchanging environment showed that behavioural and psychological factors played an important role in the causation of essential hypertension. Studies linking chronic mental stress at work place to hypertension(Gamage & Seneviratne, 2016), and hypertension in migrants (Kusuma et al., 2009) adds to the importance of stress and need for preventive measures. The study by the Baker Heart Research Institute group identified the stress biomarkers in patients with essential hypertension, shifting the focus from epidemiological studies to stress hormone related approach. (Esler et al., 2008). The absence of such biomarker in those without hypertension further strengthened the link between stress and hypertension.

## **STRESS AND RESPIRATORY HEALTH**

Stress resulting in exacerbations of allergic diseases is a well-known entity since ancient times, which made respiratory diseases like asthma to be referred to as psychosomatic illnesses (Yoshihara, 2015). Considerable amount of research has

commenced in this area and current models focus on psycho-neuro-immunology to explain the links between psychological stress and allergic diseases. Allergic diseases are known to be triggered by both internal and external stimuli. There is a growing evidence of psychosocial stress, including early life prenatal maternal stress being involved in programming of lung function and airway inflammation. Immune dysregulation resulting in imbalance between humoral and cellular immunity (IgE, Th1 and Th2 cells), hypothalamo-pituitary adrenal axis (HPA) involvement causing glucocorticoid injury to the airways, and the enhancement of the sympathetic nervous system (SNS) resulting in bronchoconstriction have been proposed as mechanisms for the association of stress and allergic diseases, particularly asthma (Marshall, 2004). Animal studies have also established the effect of stress on airway inflammation and airway hyper-responsiveness. A study done by Forsythe and co-workers in Canada (methacholine exposure in murine model of asthma) showed opposing acute and long-term effects on airway inflammation. The study revealed that repeated exposure to stress over the long term engages different mechanisms when compared to short-term stress and exacerbates the chronic inflammatory response of the airway (Forsythe et al., 2004).

Epidemiological research has shown adverse outcomes of psychosocial stress operating at multiple levels such as individual, familial and community, on asthma and other allergic diseases (Wright, 2011) exemplified through extant research examples, provide insight into the role of stress in the expression of asthma and other allergic disorders. Biological, psychological, and social processes interact throughout the life course to influence disease expression. Studies exploiting a child development framework focus on critical periods of exposure, including the in utero environment, to examine the influence of stress on disease onset. Early stress effects that alter the normal course of morphogenesis and maturation that affect both structure and function of key organ systems (e.g., immune, respiratory). Methodological disparities have been documented in the studies done and hence a recent review acknowledges the need for innovative methodologies that document pathways associated with stress at multiple levels. Also, evaluation of potential interventions that mitigate the impact of stress upon asthma morbidity are needed to address persistent disparities in asthma within racial/ethnic minority and economically disadvantaged communities (Yonas et al., 2012).

Stress has been associated with morbidity in chronic respiratory illnesses such as asthma, chronic obstructive pulmonary disease (COPD) and other allergy

associated respiratory disorders where 75% of physician consultations occur due to allergy related conditions(Marshall, 2004). 20% to 35% of asthma patients show exacerbations during stress. Symptom perception, emotional triggers and other psychological factors such as anxiety and depression have been shown to be factors for exacerbation of respiratory symptoms in COPD and asthma patients (Laube et al., 2003). Depression is at least 2 times more common among patients of severe COPD when compared to those with mild COPD. (Yohannes & Alexopoulos, 2014). Interventions aiming at reduction of effects of stress would pave way for better outcome of chronic respiratory illnesses.

## **STRESS AND NEUROLOGICAL HEALTH**

Neurological illnesses are affected by the presence of stress. The pathology of stress on neurological illnesses ranges from adverse effect on neurogenesis to neuronal inflammation to epigenetic modifications of gene expression (Schoenfeld & Gould, 2012). Studies have highlighted the co-morbidity of stress with various neurological illnesses, mainly headache, multiple sclerosis (MS), Parkinson's disease (PD), epilepsy and stroke (Keynejad et al., 2019)psychiatry and neurology, functional neurological disorder (FND. We shall not include the neurodegenerative disorders and the psychogenic movement disorders in our discussion here in this chapter.

### **Stress and Headache**

Stress plays both an independent and interactive role in primary headaches such as tension type headache (TTH) and migraine. Studies have tried to establish stress as a factor for multitude of events during the course of headache. Stress can act as a predisposing factor for onset of headache in vulnerable people, it can hasten the progress of head ache from being episodic illness to continuous chronic illness, it can precipitate individual episodes of headache and it can also worsen the quality of life among those suffering from headache. In addition to all of the above, cycle of headache and stress can be considered as a **vicious cycle**, with one worsening the other and significantly impacting the sufferers wellbeing(Cathcart et al., 2010). Stress has been reported as the most common trigger for tension type headache(Hassan & Asaad, 2020).

Recent review suggests that stress has been shown to activate NF $\kappa$ B which leads to activation of iNOS and COX2 which are involved in pain pathways. A normal stress response involves initial activation of the HPA axis, which is known

to elevate glutaminergic excitation in the central nervous system (CNS). Hence, increases in glutamate and other cytokines may activate NMDA receptors and other second-messenger pathways, leading to NF $\kappa$ B activation, iNOS elevations, and NO production, which result in both vasodilatory changes and oxidative changes. This may lead to pain generated from intracranial vessel dilatation, dura, and other structures, which if persistent, may cause TTH and potentiate pain in pericranial muscles by means of peripheral and central sensitization (Munhoz et al., 2008). The biological interaction between stress and migraine can be explained at multiple levels. Large scale studies such as SMILE and PAMINA study have reported the stress to be a common accompaniment of migraine (Radat et al., 2008). Chronic stress through its activation of NMDA and  $\mu$  opioid receptors induces hyperalgesia. Stress also affects the immune system and activation of inflammatory mediators such as Tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), Interleukin (IL) 1 $\beta$ , IL-6 and nitrous oxide, which can sensitize the pain matrix. The stress and migraine interaction has been proposed as a model disease of allostatic load (Borsook et al., 2012) allostatic responses can become dysregulated and maladaptive (“allostatic load”). Stress can thus act as a trigger for onset of migraine, can predispose a patient who is genetically vulnerable, can serve as a factor for transformation into chronic migraine, and the recurrent attacks itself predispose the patient to stress (Sauro & Becker, 2009)”

### **Stress and Seizures**

There is a clear bidirectional relationship between seizures and depression which has been proven in multiple studies (Kwon & Park, 2014). Disrupted adult neurogenesis is a common feature of both disorders, raising the possibility that altered neurogenesis might contribute to this bidirectional relationship. Chronic reductions in neurogenesis following stress and depression would reduce the number of normal granule cells present in the dentate gyrus. A relative paucity of normal granule cells prior to a subsequent epileptogenic insult could magnify the disruptive potential of abnormal cells generated after the insult. However the biological relationship has been difficult to establish between stress and epilepsy (Danzer, 2012) . Thapar et al in his longitudinal observation found that depression mediates the relationship between stress and anxiety and change in seizure recency and seizure frequency (Thapar et al., 2009). Perceived stress is high among patients with epilepsy (Moon et al., 2016).

There have been discussions regarding stress being one of the factors contributing to premature mortality in people with epilepsy however currently the evidence is meagre to make such associations (Yuen et al., 2007). Nevertheless, stress management in case of seizures would be beneficial for adequate seizure control which is the ultimate therapeutic goal to be attained.

### **Stress and Parkinson's Disease**

Chronic stress has been proposed to trigger Parkinson's disease (PD). Theories proposed based on findings in animal studies are stress induced activation of HPA axis causing glucocorticoid injury, reduction of regulatory T lymphocytes and increase in extracellular dopamine causing oxidative injury - all resulting in striatal damage and neuronal degeneration in susceptible individuals (Djamshidian & Lees, 2014). In humans, motor symptoms appear only after 70–80% of striatal dopaminergic content is lost, likely due to compensatory mechanisms in the remaining neurons. Preclinically, there may be manifestations of non-motor symptoms resulting from stress response dysfunction caused by the ongoing dopamine loss. The malfunction of the stress system could lead to an accelerated neurodegeneration in a positive feedback-type scenario (Hemmerle et al., 2012)

### **Stress and Multiple Sclerosis**

The association of stress and Multiple sclerosis (MS) has been shown in a recent systematic review(Briones-Buxassa et al., 2015)Scopus, and PsycINFO databases were searched for relevant articles published from 1900 through December 2014 using the terms “stress\*” AND “multiple sclerosis.” Twenty-three articles were included. Studies focused on the effect of stress on multiple sclerosis onset (n=9. However, no studies till date have established a causal relationship between them. Biological and psychological models both have been proposed for inflammatory processes and relapses in MS due to stressful life events (Karagkouni et al., 2013). Life-event stress impacts to a small degree on MS relapse. The number and not the severity of acute stressors are most important; chronic stressors do not predict later relapse. MS patients should be encouraged to reduce acute stressors during times of high stress and feel reassured that disease related chronic stressors do not increase their relapse risk. The MS patients should avoid situations that are likely to generate multiple stressors or which provide few avenues for social support (Brown et al., 2006)disease, demographic, psychosocial and lifestyle factors.\nBACKGROUND: Relatively little attention has been paid to the role of non-clinical relapse predictors (other than stressful life-events.

### **Stress and Stroke**

Stress and prolonged HPA axis activation could prove deleterious. Glucocorticoid exposure is a critical determinant of stroke outcome; prior exposure to stress and elevated **peri-ischemic** glucocorticoid concentrations are associated with poor outcome among stroke patients and in rodent models of cerebral ischemia. Likely, stress and glucocorticoid exposure exacerbate stroke by sensitizing the neuroimmune response to ischemia (Stuller et al., 2012).

Thus, it is crucial to understand the relation of stress to neurological illnesses for holistic management of these conditions and develop treatment strategies to ameliorate its negative impact on disease progression and prognosis.

## **STRESS AND ONCOLOGY**

There is a strong evidence for links between bio-behavioural risk factors such as chronic stress, depression and social isolation and cancer progression in epidemiological, physiological and molecular studies. By contrast, there is only limited evidence for the role of these behavioural factors in cancer initiation (Lutgendorf & Sood, 2011). The stress response involves activation of SNS and HPA axis and neuroendocrine pathways resulting in the release of glucocorticoids, catecholamines, and pro-inflammatory cytokines such as IL-1, IL-6, and TNF- $\alpha$  (Powell et al., 2013). In both animal and human studies, chronic stress has been shown to decrease cellular immune parameters, such as natural killer (NK) cell cytotoxicity and T-cell responses to mitogen stimulation. A review has suggested the neuroendocrine impact of chronic stress on the biological processes of tumorigenesis (Thaker et al., 2007).

A modest association could be identified between death of spouse and breast cancer risk in a metanalysis. (Duijts et al., 2003). Association of breast cancer and stress has been shown to have modest evidence in cancer progression however the evidence in initiation of cancer is lacking (Antonova et al., 2011). Stressful life events, death of spouse and death of relative or friend having odds ratios of 1.77 (95% CI 1.31–2.40), 1.37 (95% CI 1.10 –1.71) and 1.35 (95% CI 1.09 –1.68) respectively showed a statistically significant effect on breast cancer risk (Duijts et al., 2003). The conclusion which can be drawn is that there is a significant diversity in the findings between the studies.

Stress has been shown to have adverse impact on multiple other cancers such as hepatocellular carcinoma, head and neck cancer, ovarian cancers, etc (Lutgendorf

& Sood, 2011). But the research in these areas is sparse to allow us a comprehensive understanding. On similar lines, cancer treatment and survival can also be the source of stress which influences the long term health outcomes(Andrykowski et al., 2008). Caregivers experience poor psychological health, including elevated levels of emotional distress and anxious symptoms, relative to patients and the general population. Caregivers also report considerable perceived burden and care giving-related strain as shown in a review (Longacre et al., 2012).

## **STRESS AND DERMATOLOGY**

Skin and nerves are both derived from the ectoderm. This common derivation appears to be responsible for the intricate relationship between the brain and skin. The neuro-immuno-cutaneous-endocrine model by O'Sullivan et al explains the complex relationship between the mind and the skin (O'Sullivan et al., 1998). Psychosocial stress precipitates and or exacerbates various dermatological conditions. The constant interplay between the central and peripheral HPA axis and release of corticotrophin releasing factor (CRF) from sensory nerves and immune cells in response to emotional and environmental stressors (Slominski et al., 2013), has been shown to be associated with the disease activity in common skin disorders such as psoriasis, atopic dermatitis, urticaria, alopecia areata, acne and skin tumors (Kim et al., 2013). Psychosocial stress can also result in epidermal barrier dysfunction (Choe et al., 2018), increase in neuropeptides such as Neuropeptide Y (Madva & Granstein, 2013), increase in Th2 cellular responses and cytokines such as IL4, IL5 and IL13 and mast cell activation (Dhabhar, 2013) , which are responsible for symptomatic flares in chronic dermatological inflammatory conditions such as atopic dermatitis.

The course of certain dermatological conditions such as psoriasis, acne, alopecia areata and many other disorders is influenced adversely by the presence of psychological stress (Peters et al., 2012). A comprehensive review has described the role of psychological factors in onset and exacerbation of psoriasis (Rousset & Halioua, 2018). A study done in India showed stressful life events in 26% of the patients in the psoriasis vulgaris group and 16% of the patients in the chronic urticaria group within 1 year preceding onset or exacerbation of skin disease (Malhotra & Mehta, 2008). Atopic dermatitis is also a chronic inflammatory skin disease where a cross talk between brain, immunity and endocrine system plays a vital role in symptom exacerbations. Psychological stress through its direct and indirect effects on immune response, cutaneous neuropeptide expression, and skin

barrier function, has become a significant contributor to the disease course of atopic dermatitis (Suárez et al., 2012)..

Some dermatological conditions, being chronic illnesses, bear a significant effect on quality of life. Patients experience psychological distress and social disability. Dermatologists need to be sensitive enough to recognize the underlying stressors and address them for comprehensive management of the skin disorders (Yadav et al., 2013).

## STRESS AND IMMUNE SYSTEM

Psychoneuroimmunology is a relatively new concept, which tries to explain the mechanisms involved between stress and its effect on the immune system. Acute stress is known to have protective effect against infections however multiple studies have shown that chronic stress downregulates the immune system (Straub & Cutolo, 2018) Stress has its effects on both innate and adaptive immunity.

Chronic stress affects the immunity through the following mechanisms:

- a) the strongest evidence for the role of prenatal and early life experiences on immune function comes from animal models. Maternal stress also affects placental transfer of antibodies from the mother to the neonate. Decreased maternal transfer of antibodies may affect the neonate's ability to fight infection (Fagundes et al., 2013)
- b) Immunosenescence associated with aging has been a known entity. Chronic stress in elderly caregivers of people with chronic illnesses such as dementia or caring for children with chronic illnesses has shown to have increased levels of IL6, impaired natural killer (NK) cell functioning, thereby making them more prone to infections and inflammatory diseases (Heffner, 2011)
- c) Immune modulation by the “stress hormones” secreted by the HPA axis and SNS can proceed in two ways, either directly through binding of the hormone to its cognate receptor at the surface of a cell or indirectly by inducing dysregulation of the production of cytokines, such as interferon- $\gamma$  (IFN- $\gamma$ ), IL-1, IL-2, IL-6 and TNF (Glaser & Kiecolt-Glaser, 2005)

- d) Stress has its effect on cellular immunity- dysregulation in NK cells, macrophage and T cell functioning (Dragoş & Tănăsescu, 2010) and altered response to vaccinations because of the increase in corticosterone (CORT) causing defective functioning of antigen presenting cells and increase in IL-6, an inflammatory mediator, shown in most animal and some clinical studies and (Powell et al., 2011) e) Telomere shortening of the T cells has been shown in both preclinical and clinical studies. This occurs in response to early life stress and also shown to prevail across the lifespan resulting in premature senescence of the T cells. This can also result in reactivation of latent viral infections such as Herpes simplex virus-2 (HSV-2) (Price et al., 2013).

Psychological stress in Human Immunodeficiency Virus (HIV) can be taken as a model to explain the effect of stress on immune function and how the outcome of the illness is influenced by stress. Sensitivity analyses show that personality types or coping styles and **psychological** distress were more strongly associated with greater HIV disease progression than stress stimuli per se, and that all of the immunological and clinical outcome indicators (acquired immunodeficiency syndrome stage, CD4+ T-cell decline, acquired immunodeficiency syndrome diagnosis, acquired immunodeficiency syndrome mortality, and human immunodeficiency virus disease or acquired immunodeficiency syndrome symptoms) except viral load exhibited detrimental effects by adverse psychosocial factors (Chida & Vedhara, 2009). However, mechanisms underlying the same have not been entirely established. Also, it is shown that positive psychological factors such as positive beliefs (optimism, finding meaning, spirituality), positive affect, positive behaviours (expressing/processing emotions, proactive coping, adherence, etc.), active ways of interacting (openness, extraversion), and fostering social support can help a person with HIV to cope and to remain engaged in living (Ironson & Hayward, 2008).

## **STRESS AND ENDOCRINOLOGY**

Stress has its effects on various neuro-endocrinological pathways resulting in impaired hormonal regulation. Here again, HPA axis and immune systems are the key mediators. Diabetes mellitus, eating behaviours, obesity, autoimmune thyroid disorders such as Graves disease and polycystic ovarian syndrome are some of the endocrine disorders which would be described here.

### **Stress and Diabetes Mellitus**

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia. The lacunae in understanding the influence of psychological stress on diabetes stems from the heterogeneity of the disorder, complex interactions of multiple systems, inability to study by adjusting for the confounders and varied meaning that “stress” carries. When it comes to causation, the quantification of the contribution of psychological stress varies with some subtypes having higher heritability and some with more environmental factors. Psychological stress can result in varied coping patterns with higher prevalence of avoidance and emotionally focused coping skills in patients with diabetes (Sobol-Pacyniak et al., 2014). Coping behaviours such as lack of physical activity, smoking, lack of adherence etc are all independently known to increase odds of developing the illness or worsen the overall outcome of the treatment. Stress levels in type 1 DM is significantly higher and is known to have an adverse influence on metabolic control. Impaired post stress recovery in systolic and diastolic blood pressure, heart rate and cholesterol, and blunted stress reactivity in systolic blood pressure, cortisol, cholesterol, and IL-6 are noted in patients with type 2 DM (Steptoe et al., 2014). The association of syndrome of depression and diabetes is beyond the scope of this chapter. Due to multifactorial causation, non-reducibility to a linear causation and the systemic interactions involved in causation, at present our understanding of the role of psychological stress in causation is as primitive as the understanding of physiological stress being the final common pathway observed by Hans Selye. However, there is a significant positive correlation between the occurrences of the two.

### **Stress and Obesity**

Another endocrine and metabolic disorder is obesity which has links with psychological stress. In the case of ongoing psychological stress, however, chronically elevated glucocorticoids can lead to chronically stimulated eating behaviour and excessive weight gain. Repeated bouts of minor daily stressors that keep the stress system in a chronically activated state may alter brain reward/motivation pathways involved in wanting and seeking hyperpalatable foods and induce metabolic changes that promote weight and body fat mass. Activation of this circuitry can also interact with the HPA axis to suppress its further activation, meaning not only can stress encourage eating behaviours, but eating can suppress the HPA axis and the feeling of stress (Sominsky & Spencer, 2014)there is a corticotropin-releasing-hormone (CRH).

### **Stress and Autoimmune Thyroid Disorders**

Stress is considered one of the exogenous factors for onset and progression of autoimmune thyroid disorders. However systematic experiments are lacking in this area to explain the causality. Exacerbations observed clinically in Grave's disease patients in response to stress paves way for including stress based management into routine pharmacological treatment (Falgarone et al., 2013).

### **Stress and PCOS**

Evidence from biochemical, physiological, and functional studies in animal models and in humans strongly suggests that chronic stress increases ovarian sympathetic nerve activity leading to changes in follicular development, producing non-cyclic anovulatory ovary and cysts. Chronic activation of HPA pathway could affect ovarian functioning, warning of the importance to control stress in these patients to decrease its impact in the maintenance of polycystic ovarian syndrome (PCOS) and its well-recognized metabolic complications (Basu et al., 2018) leading to metabolic dysfunction and body composition alterations. Salivary amylase and cortisol are major stress mediators that have been implicated in PCOS. However, their role in altering body composition in PCOS is yet to be deciphered.

Aim:  
The present study aimed at understanding the relation between stress-associated factors and alterations in body composition among PCOS patients.

Design:  
This study enrolled a total of 100 patients (PCOS).

## **STRESS AND GASTROINTESTINAL HEALTH**

Brain gut axis is formed by the bidirectional interaction between the enteric nervous system and the cholinergic and sympathetic nervous system. Chronic stress can result in alterations in this central stress response system resulting in dysregulation of the gastrointestinal system. Stress and its link to visceral pain has been under research through decades now and well proven animal models have been proposed (Larauche et al., 2012). The key mediator involved is corticotrophin releasing factor (CRF). Stress increases the intestinal permeability to large antigenic molecules. It can also lead to mast cell activation, degranulation and colonic mucin depletion. A reversal of small bowel water and electrolyte absorption occurs in response to stress. Stress also leads to increased susceptibility to colonic inflammation, which can be adaptively transferred among rats by sensitized CD4+ lymphocytes (Konturek et al., 2011) which is defined as an acute threat to homeostasis, shows both short- and long-term effects on the functions of the gastrointestinal tract. Exposure to stress results in alterations of the brain-gut interactions ("brain-gut axis").

Active investigatory areas are functional bowel disorders, inflammatory bowel disease (IBD), peptic ulcer disease (PUD) and gastro-esophageal reflux disease (GERD). Management of stress is important in these GI disorders as studies have shown relationship between symptom exacerbations and exposure to stress. We have excluded functional gut disorders here as they border between medical and psychiatric models.

The causal link between stress and IBD has been controversial. Earlier studies have shown that psychological stress cause flare ups in IBD and studies have shown comorbidity of depression and anxiety with IBD. Stress alters intestinal permeability and increase in mast cell numbers in the mucosa (Schoultz et al., 2013) published, peer reviewed studies relevant to the topic and published in English from inception to November 2012. The databases MEDLINE, EMBASE, CINAHL and PsychINFO will be systematically searched. The search terms will include: inflammatory bowel disease, Crohn's disease, ulcerative colitis, psychological stress, mental stress, life stress, family stress, hassles, social stress, coping, mood disorders, anxiety and depression in sequential combinations. Studies will be screened according to predetermined inclusion and exclusion criteria by two reviewers. We will include clinical prospective cohort studies of all human participants aged 18 years or over with a diagnosis of inflammatory bowel disease. All eligible papers will be independently and critically appraised using the Critical Appraisal Skills Programme (CASP).

Stress as an etiologic factor might help explain the rising trend of ulcer disease and its complications in the large proportion of patients with non NSAIDs, non-Helicobacter pylori-related ulcers. Major life stress events are known to exacerbate PUD. It is more likely that stress leads to an abnormal perception of the acid refluxate rather than an increase in its volume in GERD patients (Lee et al., 2017)

## **STRESS AND RENAL HEALTH**

Evidence for this association is meagre, to draw firm conclusions. Nevertheless, stress plays an important role in the progression and complications of chronic kidney disease (CKD). The pathophysiological mechanisms state that repeated mental stressors appear to enhance SNS activity, increase glucocorticoid secretion, and potentially increase levels of inflammatory cytokines. These factors contribute to higher prevalence of hypertension, diabetes, and vascular disease, which are major risk factors for CKD. The physiologic effects may be experienced in

uterus, exerting early influences that may further heighten the adult risk for CKD. In patients with CKD, the levels of another hormone, reninase, that metabolizes products of the SNS, are lower (Bruce et al., 2009). Therefore, it is plausible that the long-term psychological stressors result in unchecked increased sympathetic nervous system activity once CKD develops, which sets in motion a vicious cycle.

However, the relationship between stress and chronic diseases such as CKD has not been pursued extensively. One factor contributing to the paucity of research in this area is that stress is a multidimensional concept that has yet to be definitively and comprehensively operationalised.

## **STRESS AND RHEUMATOLOGY**

Stress has been considered as the risk factor for pathogenesis of systemic inflammatory rheumatic diseases such as Rheumatoid Arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis, systemic sclerosis, or systemic lupus erythematosus (SLE).

### **Stress and Rheumatic Diseases**

The HPA axis and the SNS activation during chronic stress cause major inflammatory pathologies which can result in onset/ progression and exacerbations in these rheumatic diseases. Multiple reviews have shown a positive correlation between stress being both permissive and aggravating factor of the disease process(Finan & Zautra, 2013). However the studies have significant methodological issues and there is a need for more experimental research in rheumatic populations with controlled stress paradigms that include a follow-up with multiple evaluation points as emphasized by a review (de Brouwer et al., 2010).

## **STRESS AND OBSTETRICS AND GYNECOLOGY**

From menarche to menopause, psychological factors play a crucial role and hence psychosomatic obstetrics and gynaecology forms a major area of research for better understanding of impact of psychological stress on reproductive health (Chandra & Ranjan, 2007). Nevertheless, psychological aspects of infertility and its related various treatments (both sexes), abortion and conception, ovarian dysfunction and menopause need significant consideration for ensuring better quality of life.

Chronic hyper-activation of the hypothalamus–pituitary axis is associated with the suppression of reproductive function, growth, thyroid and immune functions

that may lead to various pathological states. In an animal model of early stress, it has been shown that stress-related events that occur during the foetal and early postnatal period may have lifelong programming effects on HPA axis functioning and different body functions with a considerable impact on disease susceptibility (Maccari & Morley-Fletcher, 2007).

Lifestyle factors such as age at which to start a family, nutrition, weight, exercise, psychological stress, environmental and occupational exposures, and substance use have substantial impact on fertility. Hence managing these modifiable risk factors can improve fertility rates. Stress and infertility has been well studied, however it's hard to decipher as to which is the cause and which is the effect. Studies have shown that stress leads to decrease in sperm counts, sperm density and morphology, reduction in testosterone and LH and disrupted spermatogenesis. Similarly, in females also, psychological stress such as anxiety and depression and work stress has been reported to be associated with infertility. Polycystic ovarian syndrome has been one of the well-studied diseases affected by psychological stress and in turn leading to infertility (Sharma et al., 2013).

Undergoing assisted reproductive technology (ART) for infertility is also known to be a source of perceived stress. There is substantial initial evidence that the psychological disposition of the parents-to-be influences their fertility and thus the outcome of fertilization techniques. A metaanalysis of 31 prospective studies on relationship between psychological factors such as stress and distress (measured as anxiety and depression) and outcomes of ART showed small but significant associations between stress and reduced chances of pregnancy. However, there are a limited number of studies and considerable between-study heterogeneity. Taken together, the influence of stress and distress on ART outcome may appear somewhat limited (Matthiesen et al., 2011).

Psychological aspects of abortion and miscarriage are difficult to review and summarize because of methodological flaws in multiple studies. The emotional aspects of the event is very complex to provide an overview (Astbury-Ward, 2008).

Menopausal transition rather than the postmenopausal period appears to confer a higher risk for depression in women. Risk factors for depression in the perimenopausal period include a prior history of premenstrual or postpartum depression, life stress, poor health, and absence of a partner (Bromberger & Epperson, 2018).

## Management

We have till now seen how stress impact medical illnesses. On a similar note, the medical illnesses have an impact on health related quality of life on both patient and caregivers. Hence it is very essential for us to design appropriate measures of stress management for improvement of the quality of life of both patients and caregivers. Interventions can be planned at multiple levels- individual, family and community. Pharmacological, Psychological and Psychosocial interventions for stress management must be integrated in the treatment processes of these medical illnesses to provide best health related outcomes. The interventions have been well studied for some illnesses and the evidence is sparse for certain physical illnesses. The management strategies however can be generalized across various medical illnesses. The review of stress management strategies adapted for chronic medical illnesses include psychological interventions such as mindfulness-based stress reduction, cognitive behavioural therapy-based stress reduction, relaxation therapies, self-help interventions and exercise and yoga. Drug targets for stress management such as immunomodulators have also been proposed. We shall provide general guidelines here which would help the clinicians for incorporating stress management measures as part of routine clinical practice.

- a) Screening should be done for stressors, perceived stress and other emotional disorders such as depression and anxiety using specific scales and self-report questionnaires.
- b) Stress management should be incorporated as one of the steps in the treatment of all chronic physical illnesses.
- c) Self-help interventions such as combined information provision with relaxation exercises, goal setting and cognitive restructuring have shown results for improvement of depression.
- d) Specific psychological interventions such as Mindfulness based stress reduction (MBSR) and Cognitive behaviour therapy (CBT) should be done whenever feasible.
- e) Yoga and exercise therapy have also been useful for stress reduction in various physical illnesses.
- f) Mindfulness based stress reduction (MBSR) is a standardized program conducted as an 8-week class with weekly sessions typically lasting **2.5 to 3 hours**. During the training participants practice: 1) sitting meditation using the breath as an anchor; 2) contemplative walking; 3) mindful movement through the use of gentle Hatha type yoga postures; and 4) the body scan in

which participants practice attention control by systematically focusing on the sensations in various parts of the body. Near the end of the 8-week training program, application of mindful awareness to daily activities, often referred to as “informal mindfulness practice,” is encouraged. Mindfulness activities are practiced both in class and as homework. Audio recordings are provided to support home practice. Participants are expected to complete approximately 45 minutes of formal mindfulness practice at least 6 days per week during the eight week period. During an all-day retreat near the end of the training, participants remain in silence and have the opportunity to practice their newly acquired mindfulness skills during a sustained and uninterrupted period of time. An essential component of the weekly classes includes discussion about the experiences that occur during the practice of mindfulness both in and out of the classroom.

- g) CBT(Cognitive Behaviour Therapy) should be used for restructuring of cognitive distortions and has been well used in treatment of depression and anxiety. The addition of mindfulness into CBT helps in management of chronic pain conditions and other disorders
- h) Liaison with the mental health professionals and specific referrals when indicated to be done.

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## **STRESS RELATED AND STRESS INDUCED PSYCHOSIS**

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### **OUTLINE**

1.	INTRODUCTION	2.	NOSOLOGICAL EVOLUTION
3.	CATEGORIZATION AND NOMENCLATURE	4.	EPIDEMIOLOGY AND AETIOLOGY
5.	CLINICAL TYPES OF STRESS INDUCED/RELATED PSYCHOSIS	6.	DIFFERENTIAL DIAGNOSIS
7.	TREATMENT AND MANAGEMENT	8.	COURSE AND OUTCOME
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## **INTRODUCTION**

Stress and performance follow an inverted ‘U’ relationship as validated by the Yerkes-Dodson law, which shows that an optimum level of arousal may be required for performance that when crossed may result in unprecedented anxiety and decompensation (Cohen, 2011). The braving of stress and trauma can have a lasting impact on the psychological well-being of an individual. The intricate inter-dynamics between resilience, maladaptive coping and psychiatric illnesses is an imperative one. Engel’s biopsychosocial model highlights, albeit simplistically, the dualistic interaction of the mind and body in the background of one’s dynamic and interactional environment which includes the psychological milieu of an individual (Borrell-Carrió et al., 2004). Thus, psychosocial upheavals and resultant stress may precipitate, predispose and/or perpetuate psychiatric illnesses at large and “Stress related and induced psychosis”, in particular.

The synonyms of the above are many due to several cultural underpinnings and understandings, including reactive psychosis, etc. Reactive psychosis are reported to most commonly occur in individuals who have either a neurosis or a character disorder, fostering a vulnerability to stress related psychosis. It usually has an acute onset and close temporal relationship to an emotional trauma or adversity (Stephens et al., 1982).

**Table 1: Synonyms of Acute Psychosis across the globe**

Country	Psychosis
France	Bouffee Delirante
Germany	Motility Psychosis, Cycloid Psychosis, Reactive Psychosis
Scandinavian	Psychogenic Psychosis, Schizophreniform Psychosis
America	Remitting Schizophrenia, Good prognosis schizophrenia, Hysterical Psychosis, Acute Schizoaffective Psychosis
Japan	Atypical Psychosis
Africa	Acute Primitive psychosis, Acute Paranoid Psychosis, Transient Psychosis
West Indies	Acute Transient Reaction
India	Acute Psychosis of Uncertain Origin, Hysterical Psychosis, Acute Psychosis without Antecedent stress, Acute Schizophrenic Episode

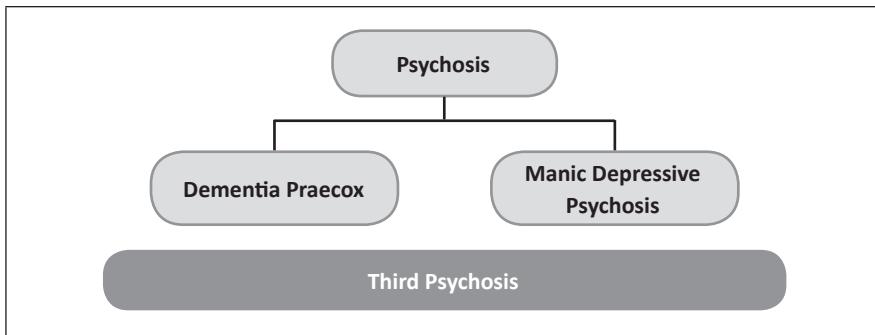
## NOSOLOGICAL EVOLUTION

*“I think, therefore I am.”*- René Descartes

The Cartesian dichotomy of mind-body dualism wherein mind and body were considered distinct and isolated entities was found to be redundant (Thibaut, 2018). The concept of “Einheitpsychose” or Unitary psychosis by Griesinger conceptualized the various spectral phenotypes of psychiatric illnesses as a manifestation of a single pathology (Berrios & Beer, 1994). However, the lack of proper explanatory models promulgated a divide in the two broad etiological models – namely the “Soma” or biological model and the “Psyche” or psychological model. The Kraepelin division of functional psychosis into dementia praecox and manic-depressive psychosis left an intermediate lacuna of a missing link on the spectrum which was known as the “third psychosis” (Craddock & Owen, 2010) and suggest that more attention should be given to the relationship between the functional psychoses and neurodevelopmental disorders such as autism. We are

entering a transitional period of several years during which psychiatry will need to move from using traditional descriptive diagnoses to clinical entities (categories and/or dimensions. Further understanding and insights were facilitated by Jaspers concept of reactivity.

Figure 1: Kraepelin's dichotomy and the concept of third psychosis.



The basic concept of reactive psychosis was mentioned in the book “**General Psychopathology**”, 1913 (Jablensky & Szmukler, 1996).

#### **Jasper’s criteria :**

Factors common to all genuine reactions –

- a. Precipitating factor- Stress should have an established temporal relationship with the reaction and should be of adequate severity to precipitate the same.
- b. There should be a meaningful connection between the contents of the experience and those of the abnormal reaction. The stress should be reflected in the psychopathology.
- c. There should be a lapse over the course of time or with the primary cause of the reaction being removed.

At this stage the definition of trauma becomes important which entails mental trauma of such nature, that psychosis would not have arisen in its absence. There may have been a predisposition of a psychopathic or neurotic nature, however, not obligatory. The close temporal relationship between trauma and onset should be established. All this should happen in the absence of any genetic link.

Jasper also classified the reactive states in different ways (Jablensky & Szmukler, 1996) –

1. *According to precipitating factors* – Prison psychosis, compensation neurosis, psychosis due to earthquakes/catastrophes/homesickness, battle psychosis, psychosis due to isolation – whether due to linguistic barriers or deafness.
2. *According to particular psychic structure of reactive state* –
  - a. Psychesthenic reactions – similar to reactive depression
  - b. Explosion, fits, tantrums, etc.
  - c. Clouding of consciousness
  - d. Puerilism, Ganser syndrome, hysterical delirium, stuporous picture, ideas of persecution
  - e. Acute paranoid reaction

*3. According to type of psychic constitution which determines the reactivity-*

There can be short lasting psychotic reactions even in a normal person.

These reactions are commoner in a person who have some kind of persistent or transient increased reactivity.

As mentioned before a constellation of different names for the acute onset, stress-related and atypical psychosis were available, with minor variations and culturally sensitive definitions.

**Figure 2: Constellation of regional variants of “Reactive Psychosis”**



Three National traditions drew major attention to these disorders:

- The French Boufee Delirante (Malhotra, 2007)
- The German Cycloid Psychoses (Leonhard, 1961)
- The Nordic or Scandinavian Reactive/Psychogenic psychoses (Bergsholm, 2016)

**Faegerman (1963) and McCabe (1975)** (Hansen et al., 1992; Retterstøl, 1986) consequent to long term studies on reactive psychosis found the following common observations –

1. an abnormal premorbid personality with high sensitivity, immaturity and lack of confidence.
2. an acute breakdown.
3. florid emotional disturbances.
4. absence of autistic features.
5. short duration of illness and a good prognosis.

In the Indian context, existence of a separate nosological entity of acute psychosis from India was made by Wig and Singh in 1967. This was identified as an acute onset psychosis with florid symptomatology and good prognosis. They pointed out equivalent nosology of Hysterical psychosis to acute psychosis of uncertain origin.

Epidemiological studies paved the way for future diagnostic identification and validity of this diagnosis. The main studies needing a mention include –

- a. **International Pilot Study of Schizophrenia (IPSS 1968-1970)** (Sartorius et al., 1974)– The study aimed at examining the characteristics of schizophrenia in different parts of the world and evaluate cultural differences if any. The variety in presentations, course and outcome elucidated differences from classical schizophrenia and another “good outcome” variant schizophrenia. Around 26% of people with schizophrenia only had one episode. Surprisingly, prognosis and outcome were more favourable in developing countries like India.
- b. **Determinants of Outcome of Severe Mental health Disorders (DOSMED 1978-1980)** (Sartorius et al., 1986)– After approximately 10 years, to reassess

the findings of IPSS, WHO conducted another study with a greater number of centres (3 being in India). The broadly defined definition of psychosis ( which included reactive and unspecified psychosis as per ICD 9) had an incidence of 1.5-4.2 lac/year whereas the narrowly defined definition reduced this number to 0.7 lac/year.

There was a group with non – affective psychosis who remitted completely. They were called NARP (Non-affective acute remitting psychosis). Four criteria could be central to the classification of this condition (Susser et al., 1996):

1. Non-affective – does not meet criteria for mood disorder,
2. Acute onset – as defined in ICD-10 acute and transient psychotic disorder,
3. Brief duration – less than 6 months from onset to recovery,
4. Psychosis is broadly defined.

Incidence of NARP was 10 times higher in developing countries. These patients from developing countries exhibited a benign course at 2 years follow up.

- c. **Cross Cultural study of – Acute Psychosis (CAP 1980-1982)** - A large proportion (41.2%) of acute psychosis patients showed Schizophrenic symptoms, whereas 20% showed affective symptoms and 35.3% other psychoses. Around 41.7% of them showed stress close to onset. There was a marked prevalence of patients from below average socioeconomic status. 2/3<sup>rd</sup> remained well with no relapses at the end of 1 year. Outcome in patients of acute Psychosis with schizophrenic symptom was similar to those with only affective symptoms.

Thus, from the above studies a separate entity was established as a plausible and possible diagnostic entity with the following peculiar symptomatic features –

1. Acute or sudden in onset
2. Variable and unstable symptomatology
3. Associated anxiety
4. Affective symptoms, most commonly fear
5. Clear relation with a stressor
6. Good premorbid adjustment
7. Rapid and complete recovery

## CATEGORIZATION AND NOMENCLATURE

Why categorize?

- Pathogenesis reflects that there are some fundamental differences in etiology between the cases that react with a psychosis and those that undergo a neurotic reaction.
- Psychoses may lead to admission to inpatient facilities and further treatment.
- Unless categorized there will be difficulties and problems with differential diagnosis.

The understanding of nomenclature may be better understood through the two main classificatory systems namely the Diagnostic and Statistical Manual (DSM) and International Classification of Diseases (ICD).

**Table 2: Current diagnostic differences between ICD 10 and DSM 5**

<b>ICD-10</b> <b>Acute and Transient Psychotic Disorder</b>	<b>DSM- 5</b> <b>Brief Psychoses</b>
1. An acute onset (within 2 weeks) as the defining feature of the whole group;	1. Duration of an episode >1 day <1 month.
2. The presence of typical syndromes;	2. Presence of one (or more) among: delusions/hallucinations /disorganized speech/catatonic behavior.
3. The presence of associated acute stress.	3. With/without stressor/postpartum onset (within 4 weeks)
4. Along with these, there are diagnostic guidelines which include the following: <ul style="list-style-type: none"> <li>• Should not meet criteria for manic or depressive episodes although affective symptoms may be present.</li> <li>• Absence of organic causation although perplexity, confusion and inattention may be present.</li> <li>• Absence of obvious intoxication by drugs or alcohol.</li> </ul>	4. Not accounted by mood disorder with psychotic features, schizoaffective disorder, or schizophrenia and is not due to the direct physiological effects of a substance/ general medical condition.
	5. Full return to premorbid level of functioning.

**DSM** (American Psychiatric Association, 2013) – an overall paradigm change in understanding from brief reactive psychosis which included depressive reaction, reactive excitation, reactive confusion, acute paranoid reaction (DSM-II) gradual addition of sudden onset (< 2 weeks) and presence of precipitating factors (DSM-III). Separation and individuation from Schizophreniform disorder and renaming as “Brief Psychotic Disorder” with or without marked stressor (DSM – IV).

**ICD** - First appeared in ICD 8 as ‘Other Psychosis’ including reactive depression, reactive excitation, acute paranoid reaction and unspecified reactive psychosis. In ICD 9, accommodated under the heading of ‘schizophreniform reaction and other non-organic psychosis’.

ICD 10 diagnosis related to stress induced psychosis include –

- **Acute polymorphic psychotic disorder without symptoms of schizophrenia** (F 23.0) Includes: cycloid psychosis and bouffee delirante.
- **Acute polymorphic psychotic disorder with symptoms of schizophrenia** (F 23.1) Includes: cycloid psychosis and bouffee delirante.
- **Acute schizophrenia-like psychotic disorders** (F 23.2). Includes: Acute schizophrenia, Brief schizophreniform disorder and psychosis oneirophrenia, Schizophrenic reaction.
- **Other acute predominantly delusional psychotic disorders** (F23.3) Includes: Paranoid reaction, Psychogenic paranoid psychosis.,
- **Other acute and transient psychotic disorders** (F 23.8),
- **Acute and transient psychotic disorder, unspecified** (F 23.9).

**Polymorphic presentation** includes fleeting hallucinations and delusions, mood instability, agitation, fluctuating anxiety symptoms, and **few negative symptoms**.

**ICD-11** has done away with the non-polymorphic variants

- Simply subtypes ATPD as either single-episode or recurrent.
- Remission of symptoms within 3 months.

Thus, from the current classificatory systems we can differentiate between the erstwhile Kraepelin dichotomy and identify a separate diagnostic entity.

**Table 3: Differences between Schizophrenia, Third psychosis and Affective disorders**

Criteria	Schizophrenia	Third Psychosis	Affective Disorder
Duration	1 month or more	2 weeks or less	Mania - 1 weeks Depression- 2 weeks
Psychopathology	Stable	Unstable, variable, fluid and florid symptomatology	Polar or Bipolar
Psychotic symptoms	Non- Volatile	Volatile polymorphic content	Usually mood congruent
Associated symptoms	Perplexity, Ambivalence, Disturbed Volition	Anxiety	With or without associated Anxiety
Affective symptoms	NOT unless antedates affective disturbance	Fear or prominent affective symptoms	Fundamental disturbance in mood or affect
Temporal relation with stress	NOT clear	Association with a clear precipitant	Often stressful events
Premorbid adjustment	Predisposition	Good	Good
Course	Usually chronic course	Rapid and complete recovery	Recurrent

## EPIDEMIOLOGY AND AETIOLOGY

In the dearth of recent literature and neglected area of research many gaps are present in this domain. Stress induced or related psychosis comprises 15-20 % of all psychosis. The risk of morbidity maybe up to 1%. Usual demography includes females and the age group of 15-55 years, warranting attention as predispositions to societal vulnerabilities and traumatic experiences.

The course of illness has some relation to the traumatic situation. If the situation ceases, it is likely that the psychosis may subside spontaneously; if the situation persists the psychosis may not go forever but may follow a more recalcitrant course over few weeks to months. "*Time heals all wounds*", may be applicable in this scenario and may work for the person. It is the subjective experience determined by the special sensitivity of the individual at the moment of trauma and may depend on the individual's catathymic predisposition. It may hit the unprepared patient who was unable to master the situation by rational means. As time passes the event does not remain so overwhelming and intolerable, gradually attenuating in intensity.

**Etiological factors –**

1. Endogenous factors – High on neuroticism, psychopathy, maladaptive coping, weak psychological resilience.
2. Genetic factors – not much known. Family members with neurotic or psychopathy traits may be at higher risk. Family history of psychosis may predispose.
3. Personality – premorbid or family history of emotional instability, sensitive, shy, introvert, conduct issues.
4. Exogenous factors – Trauma and stress are most important.
  - a. Impersonal experiences – Catastrophes, war.
  - b. Social disasters – economical loss, conflict with law, crime, imprisonment.
  - c. Conflict within family
  - d. Sexual conflicts
  - e. Isolation, disruption of communication
  - f. Inner conflicts – conflicts of conscience, sudden blow to self esteem

Important here may be to contextualize the current ongoing **COVID-19 pandemic** (Montes de Oca Rivas et al., 2020), which may, if not create but bring forth, many etiological factors. Cases of reactive psychosis have been noted and reported. In a pandemic, with infection as contagious as misinformation, feelings of fear and uncertainty may loom large. The enmeshment of stress, sleep deprivation, depression, anxiety, and fear in patients, family members and largely overlooked, frontline health care workers may wind the fire of an impending breakdown and resultant psychosis.

## **CLINICAL TYPES OF STRESS INDUCED/RELATED PSYCHOSIS**

Types of psychosis should be determined by the type of emotional trauma(Jablensky & Szmukler, 1996).

- A. *Reactive depressive psychosis:* Approximately 65 % of all cases. Often occurs in individuals with a prior history of neurosis. As a rule, the onset is sudden and follows an emotional conflict. The symptoms in addition to depressed mood, centre around the conflictual situation. Individual is rarely self-deprecatory and can think of little other than the conflictual situation. There is also loss

of appetite and weight, tiredness and irritability in the absence of prominent psychomotor retardation. Sleep disturbances usually consist of initial insomnia. Evening worsening of mood is found. Anxiety maybe the predominant symptom in some. The disorder is usually short lived. Reactive excitations are comparatively uncommon. It becomes important to differentiate it from affective psychosis.

**Table 4: Differences between Reactive Depressive Psychosis and Manic Depressive Psychosis**

	Reactive Depressive Psychosis	Manic Depressive Psychosis
Premorbid Personality	Neurotic	Cyclothymic
Heredity	Uncertain	Family history of depression or mania
Onset	Associated with severe 'understandable' trauma	No apparent trauma may be present
Thought Content	Centred around the trauma	Self-deprecatory (depression)
Psychomotor Activity	Normal	Inhibition/Excited
Mood	No distinct pattern	Diurnal variation
Sleep	No insomnia or initial insomnia	Interrupted sleep or terminal insomnia
Course	Dependent on traumatising situation, usually days to weeks.	Independent of external events, maybe up to months.

- B. *Confusional syndromes:* 15 % of all cases, having disconnected speech with predominant delusions and hallucinations, which should be understandable and related in content to the traumatic situation. The acute onset in the presence of clouding of consciousness with preserved affect is typical. Autism should be precluded.
- C. *Acute Paranoid Reaction:* Approximately 20 % of all cases. Lesser severity at onset with overall well-preserved personality and no major deterioration. Premorbid sensitive personality may be predisposing. Usually self-referential however, maintaining a good emotional contact. Also known as understandable paranoid psychosis, litigious paranoia, paranoid psychosis of prisoners. Common clinical conundrum may be differentiation of this from frank schizophrenia.

**Table 5 : Differences between Paranoid Reaction and Schizophrenia**

	Paranoid Reaction	Schizophrenia
Premorbid Personality	Personality issues, neurotic	Schizoid
Onset	Acute	Insidious
Relation with trauma	Associated with severe apparent trauma	No apparent or insignificant trauma
Affect	Good emotional contact	Blunted, autistic
Personality	Preserved	Deterioration
Psychopathology	Delusion and hallucination understandable and related to trauma	Bizarre, impossible, implausible.
Thought disorder	Absent or transient	Present
Heredity	Uncertain	Family history present

The above differentiation is vital not only due to the difference in phenomenology but also the overall course of each subtype. In

- a. Affective reaction – resolution occurs within few weeks or months
- b. Consciousness reaction – within few hours to few days
- c. Paranoid reaction – continue much longer, months to years. May become chronic (if situation does not change) or may relapse frequently.

Other interesting manifestations of reactive psychosis –

1. **Syndrome of Allers** – Seen in people who have become isolated due to linguistic barriers especially in prisoner camps. Disappears rapidly when isolation is ended.
2. **Induced Psychosis** – *Folie a deux*, usually occurring in a dyad with one dependent and other dominant individual in the background of intense proximity.
3. **Love and Romance** – “*Love is but a socially acceptable psychosis.*” Love and romantic relationship is associated with many experiences which are akin to psychotic ones. The slowing or racing of time, seeing one’s loved one in their absence, feeling their presence, hearing their voice and an altered, if

not abnormal, perception of the reality of one's environment with difficulty in rational thinking in clear consciousness is common in intense hedonistic affection towards someone or in a material world, something. This phenomenon finds place in poetry and romantic novels and not in psychiatric literature, unless there are features of De Clerambault syndrome.

## **DIFFERENTIAL DIAGNOSIS**

It is difficult to make the diagnosis of stress induced/related psychosis on the first consultation. In the polymorphic and transient picture, many a times one may not be able to elicit a temporally preceding and proximate stressor but this should not deter one from making a diagnosis rather alert an inquisitive mental health professional for missing links in his/her clinical interview. Other than different psychiatric illnesses, it is important to rule out any reversible or medical causes of behavioural impediments.

### **A. Secondary to general medical condition**

- (F00-F09) No organic mental disorder or serious metabolic disturbances affecting the central nervous system (this does not include childbirth). F05 Organic causes- consciousness.
  - Autoimmune Encephalitis
  - Epilepsy
  - Endocrine abnormalities

### **B. Substance-induced psychotic disorder**

Recent psychoactive substance-

- Intoxication (F1x.0)
- Harmful use (F1x.1)
- Dependence (F1x.2)
- Withdrawal states (F1x.3 and F1x.4)
- Delirium

### **C. If prominent affective symptoms and past history of an affective episode -**

- F30 Manic episode
- F31 Bipolar Affective Disorder
- F32 Depressive episode
- F33 Recurrent depressive disorder

**D. Stress related illnesses –**

- PTSD,
- Acute stress reaction,
- grief (depending on the duration of symptoms, severity of trauma)

E. Psychosis associated with personality disorders

F. Psychotic disorder not otherwise specified (NOS)

G. Prodrome of Schizophrenia/Psychosis

H. Schizotypal Personality Disorder

I. Schizoaffective Disorder

Perhaps the most valid differential diagnosis under the contemporary classificatory systems may be that of acute psychosis. Even though onset, duration and usual course of symptoms may be similar with broad overlap in phenomenology of symptoms, there are differentiating points between the two as studied (Kapur & Pandurangi, 1979).

**Table 6 : Differences between Reactive Psychosis and Acute Psychosis**

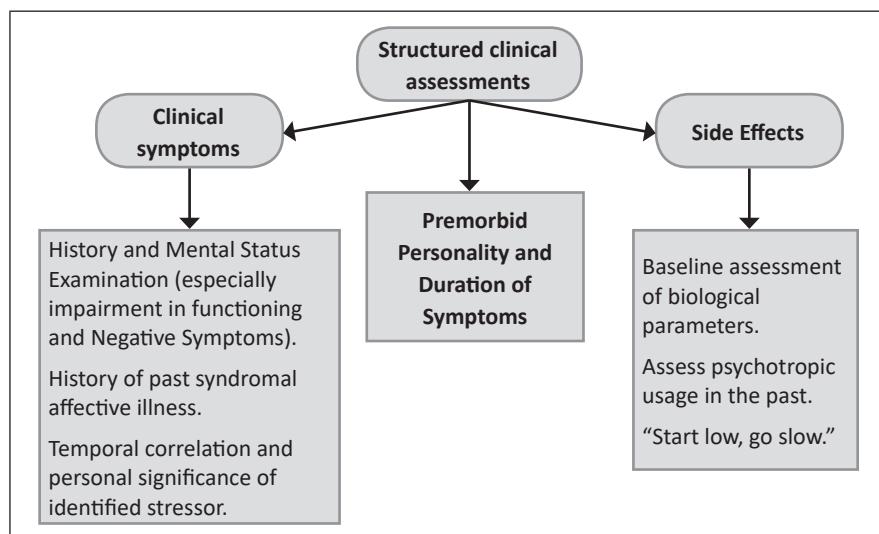
Features	Reactive Psychosis	Acute Psychosis
Behaviour	Hysterical behaviour	Impulsive behaviour
Symptoms	Affective symptoms	Tension/Worry
Mental Status	Psychomotor retardation	Withdrawal and blunted affect
Stress	More life stresses even before onset	Lesser in comparison
Personality	Premorbidly more disturbed	Lesser in comparison
Course	Less disturbed behaviour	More in comparison
Social functioning	Better	Worse
Outcome	Usually completely recover or progress into affective psychosis	Lesser likelihood to completely recover in comparison and may progress into schizophrenia.
Drug	Lower dose of antipsychotics may suffice	Comparatively higher doses may be required

Therefore, the two groups differ to a great extent in terms of phenomenology, antecedent factors and prognosis.

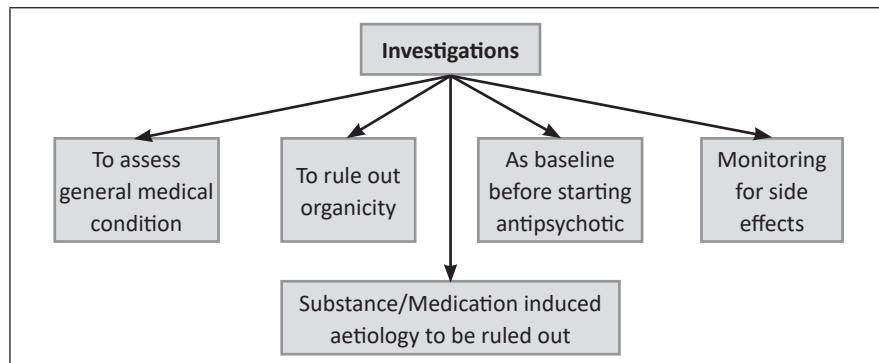
## TREATMENT AND MANAGEMENT

The first step, as in any psychiatric illness, includes a thorough clinical interview, baseline assessments and comprehensive physical examination. Imperative to reaction psychosis may be the elicitation of predating stressor of enough personal significance to precipitate the current illness. Premorbid functioning and coping styles may further contribute to an apt diagnosis. Baseline investigations including a complete hemogram, liver function test, renal function test, serum electrolytes and ideally an Electrocardiogram, before initiation may prevent any unwarranted and avoidable complications to pharmacotherapy.

**Figure 3: Assessments in a case of Reactive Psychosis**



**Figure 4: Need for baseline investigations**



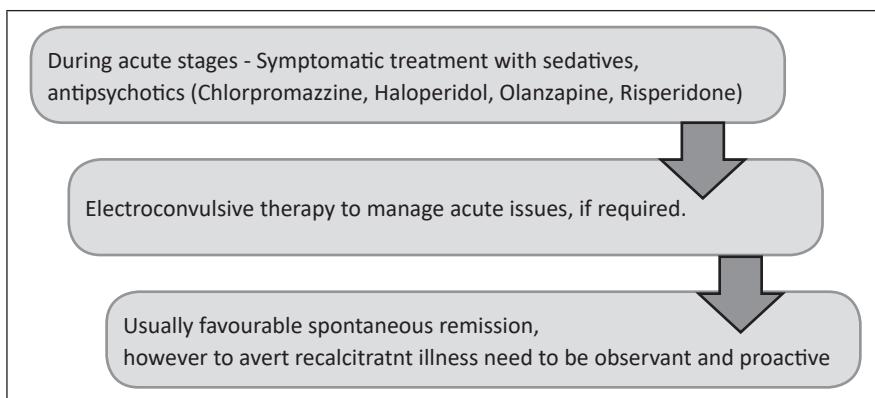
### General Principles:

- Patient and family should be involved in the choice of antipsychotics.
- Start at a low dose (patients may require lower dosage as compared to frank psychosis) and gradually up titrate to minimum effective dosage.
- Avoid using combinations thus, minimizing polypharmacy.
- Monitor regularly for side effects.
- Results of symptom improvement and side effects should be documented.

### Specific Principles:

Treatment depends on the stage of the disease and requires a holistic perspective including the pharmacotherapeutic and psychosocial parameters.

**Figure 5 : Management of acute stage of Reactive Psychosis**



Prophylactic nature of treatment when acute attack is over to prevent future relapses may be required with low dose antipsychotics and in some cases with mood stabilizers (affective symptoms).

Psychosocial interventions may focus on recognizing the cause of neurosis, strengthening of certain weak points in the personality to deal with exaggerated response to stress and facilitating the same in the patient.

## COURSE AND OUTCOME

Reactive psychosis usually has a good prognosis with complete remission. Spontaneous remissions may happen if the stress is removed or the person is

moved away from the source of stress. Psychosocial interventions are advisable to cope and deal with the stress. Risk of reactive psychosis in future is there if the stress recurs.

## CONCLUSIONS

Thus, reaction psychosis though not an established diagnostic entity in the current classificatory systems holds its diagnostic identity. Though any psychosocial stressor, potentially has the capacity to either precipitate or bring forth a psychiatric illness in a predisposed individual, yet it is interesting to note the interest, both historically and currently in the concept if “Stress induced Psychosis”. The importance is highlighted in the dearth of other similar concepts like “Stress induced Mania” or “Stress induced Schizophrenia”.

If the past has raised questions, the future shall hold the answers. A need for better understanding regarding the aetiology and treatment of this good prognosis psychosis is required. To validate the entity of this diagnosis longitudinal follow up studies with adequate sample size are needed to clearly delineate “Stress induced Psychosis” as a viable psychiatric illness which finds its place in the nosology of current classificatory systems.

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## **STRESS AND ADJUSTMENT DISORDER**

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| 11. COURSE AND OUTCOME                          | 12. CONCLUSIONS                                       |

## **INTRODUCTION**

Historically, Adjustment Disorder (AD) has been viewed as a transitional diagnostic category and, by definition, it is not an enduring diagnosis. It is presumed that the AD would not arise without the presence of stressor and symptoms of AD do not persist beyond six months after the stressor or its consequences have been terminated. The diagnostic category of AD is used widely among clinicians. AD is also considered a universally less stigmatizing psychiatric diagnosis among the public (Bourgeois et al., 2012). AD was introduced in the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-I) under the category of “**Transient Situational Personality Disorder**”. AD has been a recognised disorder for over a decade. It has been placed under ‘Trauma and Stressor-Related Disorders’ in DSM -5. The construct of AD is often criticized for the lack of scientific support, and there are

very few controlled studies in the literature to date on AD(Carta et al., 2009). In this chapter we shall review the evolution of the concept of AD, its diagnostic transition, current understanding, and its management with specific emphasis of this condition in the context of stress..

## **STRESS AND PHENOMENOLOGY IN ADJUSTMENT DISORDER**

AD is characterized by emotional or behavioural reaction / symptoms to an identifiable one or more stressful/psychosocial events (Patra & Sarkar, 2013). The stressors may be single or multiple; it may involve financial issues, other medical conditions, life events, or relationship issues. Literally, any event can qualify for a stressor by current diagnostic criteria.

The symptom complex that develops may involve anxious or depressive affect or may present with a disturbance of conduct with significant social or occupational impairment. All in all, the symptoms can be considered clinically significant by virtue of them either causing impairment in social, occupational, biological function or by being more than what would normally be expected for the given stressor. So, AD is considered as a maladaptive reaction to a psychosocial stressor. The symptom complex must not qualify for another Axis I condition (ICD -10; DSM -5).

## **NOSOLOGY OF ADJUSTMENT DISORDERS**

### **Diagnostic and Statistical Manual of Mental Disorders (DSM)**

The “Transient Situational Personality Disorder” was introduced in DSM-I in 1952, which describes the individual vulnerability during stressful situations. Further, it was subtyped as gross stress reaction, adult situational reaction, adjustment reaction of infancy, adjustment reaction of childhood, adjustment reaction of adolescence, and adjustment reaction of late-life(American Psychiatric Association, 1952). Later it was reconceptualized as “**Transient Situational Disorder**” in DSM II, thereby removing the term personality and also the emphasis of linking the presence of personality factors to the development of AD(American Psychiatric Association, 1968). In the third edition of DSM, the diagnosis of transient situational disorder was revoked and was renamed **as Adjustment Disorder**. Further, the diagnosis of AD was subtyped based on the predominant affective symptom complex. These included adjustment disorder with depressed

mood, anxious mood, mixed emotional features, disturbance of conduct, mixed disturbance of emotions and conduct, work inhibition, withdrawal, and atypical features (American Psychiatric Association, 1980). Following this, there were no major theoretical changes leading up to DSM-III-R, except that the duration of the disorder was restricted to 6 months, with the expectation of a return to baseline function or establishment of a new steady-state characterized by a more specific diagnosis. In addition, the subtype of adjustment disorder with physical complaints was added (American Psychiatric Association, 1987).

**Table -1: Nosology of Adjustment Disorder**

System	Salient feature
DSM I	Transient Situational Personality Disorder
DSM II	Transient situational disorder
DSM –III	Adjustment Disorders No requirement of severe and unusual stress as criteria, and the duration of AD was not specified
DSM- III-R	There were no major theoretical changes, except that the duration of the disorder was restricted to 6 months. Also, the subtype AD with physical complaints was added
DSM –IV	Duration of the disorder is coded as acute (less than six months) or chronic (greater than six months)
DSM-IV-TR	The stressor is identifiable but makes no mention as to what would qualify as a stressor. DSM-IV-TR describes the onset of symptoms of AD within three months of a stressor and the resolution of symptoms within six months of the termination of the stressor
DSM-5	Adjustment disorders are reconceptualized as a heterogeneous stress-response syndrome. Adjustment Disorder subtypes have been retained, without any change

\*DSM - Diagnostic and Statistical Manual of Mental Disorders

The most significant change from DSM-III-R to DSM-IV was that the disorder's duration was allowed to extend beyond the limit of 6-months imposed in DSM-III-R. The disorder's duration was coded as acute (less than six months) or chronic (greater than six months). The AD subtypes, like mixed emotional

features, work inhibition, withdrawal, and physical complaints, were eliminated (American Psychiatric Association, 1994). DSM-IV-TR stated that the stressor was identifiable but made no mention of what would qualify as a stressor. DSM-IV-TR described the onset of AD symptoms to occur within three months of the onset of a stressor and the resolution of symptoms within six months of the termination of the stressor(American Psychiatric Association, 2000; Katzman & Geppert, 2009). In DSM-5(American Psychiatric Association, 2013), AD has been reconceptualized as a heterogeneous stress-response syndrome, rather than a residual category as in DSM-IV with unchanged subtypes. Table – 1 shows a summary of the Nosology of DSM.

### **International Classification of Mental and Behavioral Disorders (ICD)**

The Clinical description and diagnostic guidelines of AD in ICD-10 are similar to the DSM 5 entity in outlining the development of psychological symptoms following a stressor. However, in ICD-10, the symptoms must appear within one month of the stressors, instead of the 3-month temporal course of DSM-5. The ICD-10 criteria share with DSM- 5 the requirement that symptoms must not persist for longer than six months after termination of stressor. The ICD-10 and DSM-5 differ in their consideration of chronicity. Whereas on one hand, the DSM-5 requires the specification of ‘acute’ or ‘chronic’ for all subtypes of adjustment disorders, the ICD-10 only refers to chronicity if the primary symptoms complex involved is that of depressed state / depression. From ICD-10 to ICD -11 (beta version), AD has been moved under the category of ‘Disorders specifically associated with stress’, and its core symptoms are similar to that of ICD-10 and DSM-5, without much change. However, in ICD -11, AD is defined with more clarity than in ICD-10, as a maladaptive reaction, which usually emerges within one month of a significant life-stressor. Two symptoms should constitute it: a) preoccupation with a stressor or its consequences; b) failure to adapt (Maercker et al., 2013). AD can be diagnosed only if symptoms do not reach sufficient specificity or severity of other mental disorders, similar to the DSM-5. The AD definition in ICD-11 gives more clarity, which facilitates AD measurement and focused treatment developments and research (Kazlauskas et al., 2018; Maercker & Lorenz, 2018). Table 2 shows a comparison of ICD 10, 11, and DSM 5.

Table- 2: Comparison between ICD-10, ICD -11 and DSM - 5

System	ICD-10	ICD -11 (beta version)	DSM -5
Category	Neurotic, Stress-related, and Somatoform disorders	Disorders specifically associated with stress	Trauma and Stressor-Related Disorders
Stressor	Present	Present	Present
Temporal course with the stressor	Symptoms of AD must appear within one month	Symptoms of AD must appear within one month	symptoms of AD must occur within three months
	Resolution of AD should not persist for longer than six months after the removal of the stressor		
Acute or chronic subtypes	Not Present	Not Present	Present
Prolonged depressive reaction	Present	Present	Not Present

\*DSM - Diagnostic and Statistical Manual of Mental Disorders

\*ICD - *International Classification of Mental and Behavioural Disorders*

## EPIDEMIOLOGY

There are few epidemiological studies on AD. In India, the National Mental Health Survey-2016 was undertaken in 12 states across six regions. The prevalence of AD was around 0.24% as per ICD-10 DCR among 34802 general population of age 18+ years (Gururaj et al., 2016). In European Outcome of Depression International Network (ODIN) study reported a 1% prevalence of AD in the general population. The higher prevalence in the ODIN study may due to the conflation of 'Mild Depression with Adjustment Disorder' (Casey et al., 2006). AD is reported to be very common in the primary care settings and has ranged from 11% to 18% (Casey, 2009). AD is also highly prevalent in medical settings like primary care, in a multisite consortium of teaching hospitals the prevalence was about 12% among 1000 patients (Strain et al., 1998). In two different studies, 50% of Cardiac Surgery patients (n= 71) (Oxman et al., 1994) and 35% of recurrence of Breast Cancer patients (n=55) (Okamura et al., 2000), had a diagnosis of Adjustment Disorder. Another large meta-analysis of 94 interview-based studies on the prevalence of AD found it to be present in 15.4% of adults with cancer in oncological, haematological, and palliative-care settings (Mitchell et al., 2011).

The prevalence of AD was found to be 10% among 11,000 patients using a DSM-III criteria at Western Psychiatric Institute clinical services. Among children and adolescents under 18 years of age, over 16 percent had AD, which is higher than other age groups. In adults, the prevalence of AD among females predominated over males by approximately 2 to 1, the difference in prevalence of AD between males and females was not so striking among children and adolescents, even though females had marginally higher prevalence than males even in this age group (Bogren et al., 2018). A study from Nepal found that 13.5% patients presenting to emergency department had clinical diagnosis of AD(Ghimire et al., 2014). The point prevalence AD was 11.5% of 636 patients from the outpatient psychiatric clinic in Duhok city of Iran(Yaseen, 2017). Table 3 shows the prevalence of Adjustment Disorder in different settings.

**Table -03: Prevalence of Adjustment Disorder in Different settings**

Settings	Prevalence
General Population	0.24 to 1%
Primary Care	11% to 18%
General Medical Care	12%
Consultation and Liaison Psychiatry	10% to 35%
Psychiatric Outpatient Clinic	10% to 11.5%
Child & Adolescent Psychiatry Clinic	16%

## **AETIOLOGY: STRESS AND ADJUSTMENT DISORDER**

‘Stress’ is defined as the mental or emotional strain or tension resulting from adverse or demanding circumstances. There are different types and severity of stressors. Stress may be a desirable or undesirable type(Paykel et al., 1971). Stressors can be of two types - eustress and distress. Eustress’ defined as positive, constructive results of stressful events and stress response (Kupriyanov & Zhdanov, 2014) and Lazarus considers eustress as a positive cognitive response to a stressor, which associated with positive feelings and a healthy physical state(Lazarus, 1993). On the other side, ‘distress,’ which is a negative stress impairs functioning (Selye, 1973). The individual’s response to stress is influenced by multiple factors. such as age, gender, health or psychiatric comorbidity, education, ethical, political, religious beliefs, etc. The presence or absence of social support, emotional support, and economic status are other factors in the family environment that can influence response to stress (Fabrega et al., 1987; Carta et al., 2009; Kocalevent et al.,

2014). Current knowledge of the association between stressful life experience and symptom development remains complex. There are few theories that have been proposed to understand the etiology in the development of AD which are discussed below.

- a) *The psychoanalysis theory* puts considerable emphasis on the context in which an event occurs before considering symptom development. The lack of an attuned response from others to stressors usually involved in AD may lead to the experience of psychological disruption(Katzman & Geppert, 2009).
- b) *The psychodynamic theory* posits a lack of experience of affect or feeling about the stressor that generates problems. Individuals who lack the opportunity to experience the feeling associated with stressors are vulnerable when suddenly exposed to psychosocial triggers, which leads to a sense of danger, anxiety and threat. It may turn inwards against self, resulting in symptoms of depression. Recent literature suggests that development of resilience to stressful events occurs during childhood that results in successful adaptation. It helps in positive self-concept, optimism, altruism, active coping style, self-regulation of emotion, and capacity to convert traumatic helplessness to learned helpfulness model (Katzman & Geppert, 2009).
- c) *Biological theorists*, McEwen and Stellar(McEwen & Stellar, 1993) coined the term “Allostatic Load” to denote the neurochemical changes following repeated stressful experiences and the capacity of the individual to cope with the same. *Allostatic load* is understood as “the wear and tear on the body” that accumulates in individuals exposed to repeated or chronic stress. This also represents the physiological consequences of chronic exposure to fluctuating or heightened neural or neuroendocrine responses resulting from repeated or chronic stress. Hippocampal Pituitary Axis, Corticotrophin Releasing Hormone, Locus Coeruleus – Norepinephrine, dopamine, oestrogen activity, lowest quartile of dehydroepiandrosterone (DHEA), neuropeptide Y, galanin, testosterone, 5HT 1A receptor, and Benzodiazepine receptor will have the highest index for a psychobiological allostatic load (Charney, 2004). Repeated exposure to stress leads to changes in multiple neuro-chemicals and their pathways like Hippocampal Pituitary axis, Corticotrophin Releasing Hormone, Locus Coeruleus – Norepinephrine, dopamine, estrogen activity, dehydroepiandrosterone (DHEA), neuropeptide Y, galanin, testosterone, 5HT

1A receptor, and Benzodiazepine receptor. The detailed discussion of the above is beyond the scope of this chapter.

## **CLINICAL FEATURES**

Diagnosis of AD requires careful consideration of the coping style of the individual, specific of the situation in which the symptoms have appeared, and self-perception of the effect of the stressor. It is characterized by emotional or behavioural symptoms formed in the context of an established psychosocial stressor/s. AD may occur in any age group; however, it is reported to be more common among the younger age group(Katzman & Geppert, 2009; Yaseen, 2017) Studies have identified school problems as the most frequent precipitant of AD in adolescents whereas in adults, marital problems are most frequent precipitants. Stressors may be single, multiple, recurrent, or enduring events. As a result, temporal and causal relationships of stressor with symptoms is difficult to establish in many cases. The commonest psychosocial stressor was the physical illnesses, followed by relationship problems and domestic problems (Yaseen, 2017).

AD with depressive symptoms as the most common type of presentation, characterized by depressed mood, low self-esteem, suicidal behaviours, increased motor activity, hyper-vigilance, impulsivity, and substance use. Additional symptoms may include a feeling of helplessness, self-blame, rejection of help, suicidal ideation, dysphoria, aggression, downheartedness, unspecific somatic complaints, loss of appetite, sleep disturbance, pain, phobic symptoms, and reduced drive. Other symptoms presentations of AD are insomnia, other vegetative symptoms, social withdrawal through behavioural symptoms and mixed presentations are seen, and suicidal thoughts /ideation. The manifestations vary and include depressed mood, anxiety, worry (or a mixture of these), a feeling of inability to cope, plan, or continue in the present situation, and some degree of disability in the day to day functioning. The individual may feel liable for dramatic behavior or outbursts of violence, but these rarely occur.

## **DIAGNOSTIC CRITERIA**

### **ICD -10**(World Health Organisation, 1992)

The diagnosis depends on a careful evaluation of the relationship between (a) form, content, and severity of symptoms; (b) previous history and personality; and (c) stressful event, situation, or life crisis. The presence of the third factor should be

established, and there should be strong, though perhaps presumptive evidence, that the disorder would not have arisen without it. If the stressor is relatively minor, or if a temporal connection (less than three months) cannot be demonstrated, the disorder should be classified elsewhere, according to its presenting features.

The conduct disorders (e.g. aggressive or dissocial behavior) may be an associated feature, particularly in adolescents. None of the symptoms is of sufficient severity or prominence in its own right to justify a more specific diagnosis. In children, regressive phenomena such as return to bed-wetting, babyish speech, or thumb-sucking are frequently part of the symptom complex. If these features predominate, F43.23 should be used. The onset is usually within one month of the occurrence of the stressful event or life change, and the duration of symptoms does not usually exceed 6 months, except in the case of prolonged depressive reaction (F43.21). If the symptoms persist beyond this period, the diagnosis should be changed according to the clinical picture present, and any continuing stress can be coded by means of one of the Z codes in Chapter XXI of ICD-10.

There should be a significant life change leading to continued unpleasant circumstances that result in an adjustment disorder. The states of subjective distress and emotional disturbance, usually interfering with social functioning and performance, and arising *in the period of adaptation to a significant life change* or to the consequences of a stressful life event (including the presence or possibility of serious physical illness). This aspect of it is discussed in an article titled “Bereavement without death” (Snow, 2017). The stressor may have affected the integrity of an individual’s social network (through bereavement or separation experiences) or the wider system of social supports and values (migration or refugee status). The stressor may involve only the individual or also his or her group or community.

**DSM – 5 (American Psychiatric Association, 2013)**

- A.** Development of clinically significant emotional or behavioural symptoms in response to an identifiable psychosocial stressor(s). Symptoms must develop within three months after the onset of the stressor(s)
- B.** These symptoms or behaviours are clinically significant as evidenced by either of the following: (1) Marked distress that is in excess of what would be expected from exposure to the stressor OR (2) Significant impairment in

social, occupational, or academic functions.

- C. The stress-related disturbance does not meet the criteria for another specific Axis I disorder and is not merely an exacerbation of a pre-existing Axis I or Axis II disorder.
- D. The symptoms do not represent bereavement (code V62.82).
- E. Once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional six months.

**Table -04: Subtype of Adjustment Disorder in ICD-10 and DSM -5**

ICD- 10	DSM -5
a) AD with Brief depressive reaction	a) AD with Depressed Mood
b) AD with Prolonged depressive reaction	b) AD with Anxiety
c) AD with Mixed anxiety and depressive reaction	c) AD with Mixed Anxiety & Depressed Mood
d) AD with predominant disturbance of other emotions.	d) AD with Disturbance of Conduct
e) AD with predominant disturbance of conduct.	e) AD with Mix Disturbance of Emotions & Conduct
f) AD with mixed disturbance of emotions and conduct Both emotional symptoms and disturbance of conduct are prominent features.	f) AD with unspecified
g) AD with other specified predominant symptoms	

\*AD- Adjustment Disorder

## DIFFERENTIAL DIAGNOSIS

The identified psychosocial stressor with sub-syndromal symptoms distinguish AD from other Axis I, Post-Traumatic Stress Disorder, and acute stress disorder as these have the nature of the stressor better characterized and are accompanied by a defined constellation of affective and autonomic symptoms. In contrast, the stressor in adjustment disorder can be of any severity, with a wide range of possible symptoms. The AD subtypes need to be distinguished from sub-threshold types of the major mental disorders, the so-called *not otherwise specified (NOS) categories*.

- a) **Depression:** Depression can be diagnosed irrespective of presence or absence of stressor if the criteria for depression are met.
- b) **Post-traumatic stress disorder (PTSD) and Acute Stress Disorder (ASD):** the stressor required for PTSD and ASD are described in detail in the criterion A of the respective diagnostic criteria, this stressor is generally extremely traumatic event and severe in intensity with specific characteristics which is not so for the stressor that precipitates AD. The timing and the severity of the symptoms are also different between AD and PTSD & ASD. AD can be diagnosed immediately following exposure to stressor and can persist up to 6 months after termination of stressor. In contrast, in ASD cannot be diagnosed if the symptoms persist beyond one month, and PTSD cannot be diagnosed within 1 month of exposure to stressor.
- c) **Personality Disorder:** Some personality disorders are vulnerability to stress and develop symptoms suggestive of adjustment disorder. The detailed longitudinal history will help us in delineating adjustment disorder from personality disorder. AD can be diagnosed even in presence of personality disorder if the stress related disturbance is more than what would be explained by the maladaptive personality traits. (i.e., Criterion C is met).
- d) **Normative stress reactions:** Many individuals get irritable and angry when things do not happen as expected by them. The diagnosis of AD should be made only if the disturbance (e.g., mood, anxiety, or behavior changes) are more than what is normally expected (which could vary in various cultures) or if there is significant functional impairment.

## COMORBIDITY

The most common psychiatric comorbidity associated with AD is personality disorders and substance use disorders. AD is associated with greater risk for completed suicide and suicide attempts. On the other hand, psychological autopsy of suicide attempter show high rate of AD retrospectively (Marttunen et al., 1994; Greenberg et al., 1995; Pelkonen et al., 2007).

## TREATMENT

AD may have sub-threshold symptomatology across various symptom domains; thus, there is no single therapeutic management strategy for the condition's

heterogeneous clinical nature(Casey, 2009). Treatment of individuals with AD requires careful consideration of the nature and severity of symptoms, taking into account the risk factors associated with higher risks, such as poor premorbid functioning and persistent stressors.

The main aim of treatment is to relieve symptoms and reach a higher degree of premorbid level of adaptive functioning. Treatment strategies should be tailored to mitigate the effect of stressors on day-to-day functioning and to enhance adaptive stress coping mechanisms. The specific treatment interventions that are considered in individuals with AD includes brief supportive counselling (De Leo, 1989), short interpersonal therapy, cognitive behavioural therapy, psychodynamic approaches(Maina et al., 2005), and integrative therapy(Lakshmi, 2017) The study from India on AD shows the integrative approach through psychoeducation, interpersonal therapy, and cognitive behavioural therapy component was found effective. It not only helps in the treatment of AD but also improves the quality of life in personal and marital life (Lakshmi, 2017).

Low-intensity psychological interventions, such as e-mental-health interventions ( telephone / video conference based) for ADs, can be a successful solution to addressing high mental-health needs associated with AD , can potentially overcome barriers, increase access to psychological interventions in ADs especially in limited mental-health resources in most countries around the world (Domhardt & Baumeister, 2018; Varker et al., 2019).

There are hardly any systematic clinical trials evaluating the effectiveness of pharmacological treatments in individuals with AD. The commonly used drugs are antidepressants and anxiolytics. Selective Serotonin Reuptake Inhibitors (SSRIs) are useful in treating certain sub-threshold depressive syndromes and can help certain sub-types of AD. Several studies of prescribing practices by physicians since the 1980s have shown a substantial rise in prescribing antidepressants (Olfson et al., 1998). However, it should be stressed that psychosocial methods remain the mainstay of treatment, with the pharmacological intervention being a supplementary form of treatment. All antidepressants are effective in the treatment of AD. None of the antidepressants were found to be more effective or superior to others in the treatment of adjustment disorder. A study showed that the combination of two classes of antidepressant was not superior to one class of antidepressant in the treatment of adjustment disorder (Looney & Gunderson, 1978). There are

non-SSRI clinical trials in adjustment disorders such as TCA, Trazodone, Ginkgo Biloba specific extract (Woelk et al., 2007), plant extracts (Euphytose), and specific extracts of kava-kava (Carta et al., 2009). However, the translation of clinical research results into real-world clinical practice has not been successful.

## COURSE AND OUTCOME

The role of age, personality style, social support networks, and comorbid conditions in influencing the path and outcome of AD has been established. Multiple studies have shown a reasonably benign course for adults, with a lesser risk of recovery in adolescents following the initial AD episode. While most adults developed major depressive disorders and alcohol abuse, adolescents reported a wide variety of major psychiatric disorders, including schizophrenia, bipolar disorder, personality disorder (Looney & Gunderson, 1978), substance abuse, and major depressive disorder (Andreasen & Hoenk, 1982). Prevalence of chronic symptoms and behavioural problems have been the most significant indicator of poor outcomes for people with AD who may also have a high risk of suicide. Comorbid diagnosis of drug abuse and personality disorder predict higher chances of suicidal attempts and completed suicide (Carta et al., 2009). Five years of a follow-up study of 76 AD patients showed an 82% favourable outcome and 17 % chronic depressive disorder (Bronisch, 1991). Readmission levels and AD-associated impairment were substantially lower than those diagnosed with comorbid drug use disorder (Greenberg et al., 1995) and affective disorder (Jones et al., 2002)..

## CONCLUSIONS

Adjustment Disorder is considered a universally less stigmatizing psychiatric diagnosis among the public. AD is a common psychiatric diagnosis in psychiatric settings. ICD -11 beta version, AD is defined with more clarity than previous ICD -10 and DSM -5. It has introduced newer concepts in the diagnosis of AD such as 1) preoccupation with stressful event and 2) failure to adapt. So, newer AD diagnostic criteria may provide diverse research findings in future studies and help to conceptualise the disorder better.

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## **STRESS & ACUTE STRESS DISORDER**

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## **INTRODUCTION**

Acute Stress Disorder (ASD), as the name itself suggests, is one of the most important sequelae of extreme stress and any discussion on consequences of stress is incomplete without its discussion. ASD was introduced as a new diagnostic entity in the diagnostic and statistical manual of mental disorders, Fourth Edition (DSM-IV) in 1994 (Bryant et al., 2011) ASD has been distinguished from post-traumatic stress disorder (PTSD) as the persistence of acute stress reactions (ASRs) was variable across the individuals who experience traumatic event ranging from spontaneous resolution in majority to development of long-term sequelae such as PTSD and enduring personality change in some patients. The establishment of ASD diagnosis was aimed to enable researchers to study the prevalence, etio-pathogenetic mechanisms, and clinicians to evaluate and intervene earlier following the trauma to prevent its progression and to give insurance coverage those who develop ASR in the 1st month after exposure to stress. It was also hoped that concept of “ASD” would help predict development of PTSD in future. (Bryant, 2018). After years of research it was found that ASD poorly predicted onset of PTSD, so this finding

lead to conceptualization of ASD as a distinct post stress disorder, subsequently necessary changes were made in the diagnostic criteria of ASD in DSM-5(Bryant et al., 2011)..

## DIAGNOSTIC CRITERIA OF ACUTE STRESS DISORDER

In the following section, authors briefly discuss about the diagnostic criteria of ICD-10 and DSM-5 nosology.

**ICD-10 (International Statistical Classification of Diseases and Related Health Problems) Chapter V Mental and Behavioural Disorders:** A transient disorder of significant severity which develops in an individual without any other apparent mental disorder in response to *exceptional physical and/or mental stress* and which usually subsides within hours or days. The stressor may be an *overwhelming traumatic experience involving serious threat to the security or physical integrity of the individual or of a loved person(s)* (e.g. natural catastrophe, accident, battle, criminal assault, rape), or an unusually sudden and threatening change in the social position and/or network of the individual, such as multiple bereavement or domestic fire.

### *Diagnostic guidelines of Acute Stress Disorder (F43.0)*

There must be an *immediate and clear temporal connection* between the impact of an exceptional stressor and the onset of symptoms; onset is usually within a few minutes, if not immediate. In addition, the symptoms:

- (a) show a mixed and usually changing picture; in addition to the initial state of “daze”, depression, anxiety, anger, despair, overactivity, and withdrawal may all be seen, but no one type of symptom predominates for long;
- (b) resolve rapidly (within a few hours at the most) in those cases where removal from the stressful environment is possible; in cases where the stress continues or cannot by its nature be reversed, the symptoms usually begin to diminish after 24-48 hours and are usually minimal after about 3 days.

**The Diagnostic and Statistical Manual of Mental Disorders – 5<sup>th</sup> edition (DSM-5)** describes the following criteria for the diagnosis of Acute Stress Disorder (ASD) (American Psychiatric Association, 2013)

**A:** Being exposed to a traumatic event (either physically, sexually or mentally)

**B:** Having more than eight of the following ASRs clustered in five categories

**(i) Intrusion symptoms:**

- Distressing memories of the traumatic event which are recurrent. Children may have repetitive game plays in themes mimicking the main event.
- Having repetitive dreams related to the traumatic event. In children, it might be in the form of night terrors.
- Enactment of the traumatic event recurrence (i.e., flashbacks).
- Intense or prolonged mental or physiological distress in response to the events or themes reminding the patient of the actual traumatic event.

**(ii) Negative mood:**

- Inability to be happy, feel successful or feel love.

**(iii) Dissociative symptoms:**

- Having a sense of being detached from self and emotions.
- Dissociative amnesia (that is not related to intoxication or traumatic brain injury [TBI])

**(iv) Avoidance symptoms:**

- Avoidance of thoughts, memories, and feelings about the traumatic event.
- Avoidance of external reminders of the traumatic event (such as people and places)

**(v) Arousal symptoms:**

- Sleep problems (such as difficulty initiating and maintaining quality sleep)
- Irritability and rage attacks with minimum to no provocation
- Highly and abnormally alert to surroundings
- Unusually strong reflexive reactive to a sudden event in the environment

**C:** Duration of the symptoms should be more than three days and less than four weeks

**D:** Symptoms must cause significant functional impairment

**E:** Symptoms must not be related to substance use or other medical conditions (such as TBI).

Criteria A to E must meet for the diagnosis of ASD.

If the duration of experiencing ASRs persists beyond four weeks, then it will meet the criteria for PTSD (Bryant, 2011). ASD has been shifted from ‘anxiety disorders’ to a newer addition ‘trauma and stressor-related disorders’ to distinguish its characteristics and emphasis the role of stress in the onset of this disorder.

Table 1 provided comparative nosology of both systems.

**Table 1: Comparative nosology - Difference between ICD-10 and DSM-5**

Characteristics	ICD-10	DSM-5
Stress-related conditions	Included under broad umbrella of “Neurotic, stress-related and somatoform disorders”	Has a separate grouping category titled “Trauma- and Stress-related disorders”, has been distinguished from anxiety, dissociative and obsessive-compulsive and related disorders
“Trauma- and Stress-related disorders”	Includes three diagnoses namely, ASD, Posttraumatic stress disorder (PTSD) and adjustment disorder	Includes five diagnoses namely, Reactive attachment disorder, social disengagement disorder, Acute stress disorder, Posttraumatic stress disorder (PTSD) and adjustment disorder
Diagnostic criteria for ASD	Included as ‘Acute Stress Reaction’ (F43.0).	Includes ASD as a separate diagnosis

### Updates in ICD-11

1. Disorders specifically associated with stress have been redefined as a separate category in ICD-11 but not part of anxiety disorders as in ICD-10.
2. In ICD-11, acute stress reaction is recognized as a normal but not a pathological entity that subsides spontaneously within few days. As a result, it has been moved to the chapter containing categories that need clinical recognition but are not defined as disorders or diseases.
3. It highlights the need to less pathologize transient emotional, cognitive, behavioral, and somatic reactions that occur commonly in the immediate aftermath of an acute stressful event. However, in order to enhance clinical as well as public health utility, the health-care workers must be trained to

recognize these reactions and offer practical psychosocial interventions without these being considered mental “disorders”

4. ICD-11 reinforces the significance of adjustment disorder as part of the continuum of stress disorders. Since there was no evidence for the validity or clinical utility of subtypes of adjustment disorder in ICD-10, these have been removed in ICD-11.

## EPIDEMIOLOGY

In general population, 20 to 90% are exposed to one or more extreme stressful events in their lifetime. About 1.3 to 11.2 percent of individuals with ASD have further developed PTSD (Perrin *et al.*, 2014).

**Prevalence of ASD** is highly variable depending on the nature of the trauma, place and timeline of assessment for ASD after the trauma.

- Specific nature of trauma:
  - ASD was diagnosed in 30% of victims who survived from injuries during the terror attacks in Mumbai, India. It was noted to be more common in females, younger age (less than 33.5 year old), divorcees and unmarried, unemployed, belonging to lower socio-economic strata, and sustained to severe injury (Balasinorwala & Shah, 2009).
  - ASD prevalence among road traffic accidents has a pooled prevalence of 15.81% (Dai *et al.*, 2018). Mothers having preterm babies had 36 folds higher chances of having ASD than those with term babies (Helle *et al.*, 2018)
- Timeline and place of assessment after trauma:
  - The prevalence rates of ASD were reported at <1-week post-injury was 24.0–24.6% and at 1–2 weeks post-injury was 11.7% to 40.6% (Ophuis *et al.*, 2018) the psychological consequences should be taken into account. There has been uncertainty regarding the prevalence of posttraumatic stress disorder (PTSD).
  - The prevalence of ASD in emergency room encounters among children exposed to trauma was 14.2% in two weeks and the prevalence of PTSD in them after nine weeks was 9.6% (Meiser-Stedman *et al.*, 2017) evaluated the revised DSM-5 acute stress disorder (ASD)

## ETIOPATHOGENESIS

### Psychological theories

The reason behind spontaneous recovery in most and development of ASD remains obscure. Several hypotheses were speculated but to “Pavlovian fear conditioning” explains this phenomenon at best(Johnson et al., 2012). If a traumatic stimulus (e.g., road traffic accident) co-occurs with a neutral stimulus (e.g., horn sound) or context (e.g., car driving), the body will have the same fear responses whenever it encounters neutral stimulus or context subsequently despite the absence of traumatic stimulus. Traumatic stimulus is conditioned stimulus and neutral stimulus and context in which trauma occurred are unconditioned stimuli

Usually, most individuals overcome fear conditioning by a gradual process of reduction in fear responses to both conditioned as well as unconditioned stimuli. This mechanism is termed as ‘extinction learning’. If it fails, the patient will continue to re-experience fearful symptoms of the initial traumatic event (Bryant, 2011)

### Neurobiological Mechanisms

AASD is understood as a resultant of allostatic disequilibrium between defensive and cognitive circuits(Allene et al., 2020). The former circuit triggers a stress response and forms an implicit memory, while the latter circuit prompts a voluntary response and forms an explicit autobiographical memory. During the initial phase of trauma, the defensive circuit, mainly Salience Network (SN) could be over-activated (Yehuda et al., 2015). Defensive behaviors manifest as hypervigilance, alteration in body’s metabolism and freezing behaviors. An increased level of vigilance via the Ascending Reticular Activating System (ARAS) helps in watching out for threat. Hyperactivity of Hypothalamic-Pituitary-Adrenal axis (HPA) within 10 minutes after the perception of threat increases the sympathetic nervous system activity and enhances gluconeogenesis and anti-inflammatory effects that provide sustained effort in combating against the threat as well as memory encoding of the traumatic events. Freezing, an involuntary, self-preserving, primary response to stress has been associated with activation of peri-aqueductal gray matter helps in preparing the individual to suspend response to threat immediately after the exposure ceases. Sustained over-activation of the defensive circuit may lead to its vicious deactivation, resulting in dissociation of consciousness and memory.

Cognitive circuit via Central Executive Network (CEN) is involved in conscious perception and assessment of danger. Thus, it aids in developing adaptive response

to the stressful situation. In ASD, the cognitive circuit is under-activated and the formation of traumatic memory gets fragmented after facing the traumatogenic situation(Kolk & Fisler, 1995)

Brain regions associated with threat detection, fear learning (or alternatively disturbed fear extinction), contextual processing, emotion regulation and executive function are found to be dysfunctional in patients who experience ASRs. The hyperarousal anxiety serves as a driver for sleep disturbances, memory and cognitive impairments, altered pain sensitivity, emotional numbing, re-experiencing, avoidance and suicidality. ASD patients with greater activation in right medial precuneus, left retrosplenial cortex, precentral and right superior temporal gyrus as well as less activation in lateral, superior prefrontal and left fusiform gyrus are associated with the development of PTSD and also of increasing severity (Cwik et al., 2017). Occurrence of dissociation and progression to PTSD are more prominent in females than in males (Kimerling et al., 2018).

### Risk factors

There is dearth of evidence that studied risk factors for developing ASD after a traumatic event. Hence, the risk factors for PTSD have been extrapolated to ASD due to their comparability in terms of experiencing ASRs and differ merely for period of occurrence of symptoms.

The risk factors can be classified into three categories (table 2) in relation to traumatic event (Sareen, 2014).

**Table 2: Risk factors for Acute Stress Disorder**

Pre-trauma factors	Peri-trauma factors	Post-trauma factors
Female gender	Trauma severity	Tachycardia
Intellectual disability	Assault	Poor socioeconomic status
Lack of education	Rape	Physical pain severity
History of traumatic events	Physical injury	ICU stay
History of psychiatric disorder(s)		Brain injury
Personality disorder(s)		Dissociative symptoms
Genetics		Disability
		Subsequent life stress

[Adapted from the review by Sareen, 2014]

## CLINICAL DIAGNOSIS

### Evaluation

ASD has no validated laboratory or radiographic test. The diagnosis is solely based on clinical history and physical examination. Careful behavioral observation, attentive listening and expression of empathy to the patient's narration of events and mental states are of vital importance value. Most patients are unable to process the trauma, resulting in difficulty to reflect upon their emotional status, subsequently present to emergency department in a state of confusion. Hence, they require more frequent consultations during the evaluation process.

There are few scales which can be used in assessment of ASD. Acute stress disorder scale (ASDS) is a validated questionnaire for adults (Bryant et al., 2000). Child stress reaction checklist (CSDC) is a validated, quick (takes 10 minutes to complete) psychometric questionnaire that examines both symptoms of ASD and PTSD and can be used for children aged 2 to 18 years old (Saxe et al., 2003).

### Differential Diagnosis

Suspected Diagnosis	Clinical Clues	Differentiating points on ASD
Post-traumatic stress disorder [PTSD]	<ul style="list-style-type: none"> <li>- Experience of ASRs following traumatic event</li> <li>- ASRs last for more than four weeks</li> </ul>	<ul style="list-style-type: none"> <li>- ASRs last for less than four weeks</li> <li>- ASD does not include self-destructive behaviors</li> <li>- ASD includes a specific category of dissociative symptoms</li> </ul>
Adjustment disorder	<ul style="list-style-type: none"> <li>- Symptoms may include ASRs but do not meet all the criteria for ASD</li> </ul>	<ul style="list-style-type: none"> <li>- Presence of ASRs amounting to syndromal criteria for ASD</li> </ul>
Brief psychotic disorder Major depressive disorder – Predominant presentation of low mood and depressive symptoms over ASRs.	<ul style="list-style-type: none"> <li>- It is stress-related</li> <li>- Lasts less than four weeks</li> <li>- Psychotic symptoms are more prominent</li> </ul>	<ul style="list-style-type: none"> <li>- Absence of psychotic symptoms</li> </ul>
Major depressive disorder	<ul style="list-style-type: none"> <li>- Predominant presentation of low mood and depressive symptoms</li> <li>- May or may not have ASRs</li> <li>- For a minimum period of 2 weeks.</li> </ul>	<ul style="list-style-type: none"> <li>- Predominantly ASRs.</li> <li>- Depressive features may or may not be present</li> <li>- Symptoms last for 3 to 28 days</li> </ul>

### **Prognosis**

- ASD patients are 24 times more likely to die from a suicide attempt compared to those without ASD. (Gradus *et al.*, 2015) yet population-based studies are few. The aims of the present cohort study were to examine the cumulative incidence of traumatic events and psychiatric diagnoses following diagnoses of severe stress and adjustment disorders categorized using International Classification of Diseases, Tenth Revision, codes and to examine associations of these diagnoses with all-cause mortality and suicide. Data came from a longitudinal cohort of all Danes who received a diagnosis of reaction to severe stress or adjustment disorders (International Classification of Diseases, Tenth Revision, code F43.x)
- Nearly 50% of patients remit within the first three months (American Psychiatric Association, 2013).

## **MANAGEMENT**

Establishment of therapeutic alliance with the victims of trauma is very essential. The evaluation and intervention go hand-in-hand right from the first contact with them (Table 2). Psychotherapy is the first line of treatment in ASD and pharmacotherapy is focused on the secondary prevention for PTSD (Howlett & Stein, 2016).

**Emergency treatment of ASDs** to those who reach emergency settings include BZDs, Crisis intervention psychotherapy, etc.

### ***Psychotherapy***

**Psychological debriefing** is a process the patient is asked to explain the trauma and their feeling about it in the first 72 hours in detail(Rose *et al.*, 2002).

**Trauma-focused Cognitive behavioral therapy** is the mainstay of treatment in ASD and has shown to be promising, particularly reducing the risk of developing PTSD (Kliem & Kröger, 2013). It includes understanding the psyche of trauma victim, symptom management skills, identifying and disputing cognitive distortions, and exposure therapy. Exposure therapy adapts the ‘fear extinction’ learning and instrumented through behavioral techniques. In this method, the patient is exposed to the traumatic source in a controlled manner to relieve the

trauma memory mimicking fear extinction. A transient worsening of the symptoms may happen in the initial few sessions

**Table 2: Approach towards patients after the experience of traumatic event.**  
[Adapted from Nash & Watson, 2012]

Ensure that they are safe after the traumatic event and educate them where to seek help in case of an emergency
Explain them that most people will have a strong emotional response that resolves in a few days or weeks and will not last longer in most conditions.
Family and friends must be explained about the prognosis, course, and coping skills for ASD.
Patients may need assistance with the police report of the incident, work leave of absence, and claiming health insurance.
Follow-up visits for the initial six months are recommended.
Evaluate them for suicidality and other comorbid psychiatric disorders in each visit
Encourage them to engage actively in planning their medical and psychological treatment
To educate and encourage patients to avoid maladaptive coping behaviors (such as drinking alcohol, self-injurious or self-neglect behaviors)

### ***Pharmacotherapy***

Evidence for pharmacotherapy in the treatment of ASD is still emerging and most of the recommendations are drawn from the trials conducted in PTSD [(Bryant et al., 2011)]. Pharmacotherapy has shown to be useful in reducing mood symptoms, but not much beneficial in alleviating recurrent memories and avoidance.

**Serotonin reuptake inhibitors (SRIs)** - Fluoxetine, sertraline, and paroxetine and venlafaxine are the first-line SRI agents (Bisson et al., 2020). Of them, Paroxetine is the only FDA approved SSRI for the treatment of PTSD. The well-tolerated, highest therapeutic dose of each of these agents can be tried for a minimum period of six weeks to ascertain its efficacy.

**Beta-blockers** - Treatment with Propranolol after an acute stressor reduces sympathetic symptoms (such as tachycardia and sweating). However, it has not lowered the chances of developing PTSD (Steenen et al., 2016).

**Benzodiazepines** - Short-term use of benzodiazepines may be considered for the sleep and anxiety related symptoms. Their long-term use is not recommended in ASD due to the risk of developing tolerance and also their ineffectiveness in the prevention of PTSD(Guina et al., 2016)

**Second-generation antipsychotics (SGAs)** - Quetiapine monotherapy is indicated when patients show minimal or poor response to SRIs and CBT(Villarreal et al., 2016). It is effective in reducing hyperarousal and re-experiencing symptoms. They should be used judiciously and must be discontinued at the earliest if no clinical response is elicited to avoid long-term detrimental adverse effects such as tardive dyskinesia.

**Psychedelics** - There is increasing use of psychedelics-assisted psychotherapy in the treatment of ASD and PTSD (Krediet et al., 2020). Cannabinoids (Canabidiol,  $\Delta 9$ -tetrahydocannabinol), Ketamine, 3,4-methylenedioxymethamphetamine(MDMA) and classical psychedelics (psilocybin, lysergic acid diethylamide) are the commonly used types of compounds so far.

### **Steroids**

Low dose hydrocortisone administration during the initial days after the traumatic event has significantly reduced the occurrence of stress reaction symptoms subsequently (Delahanty et al., 2013). It has shown to improve the autobiographical memory retrieval related to childhood trauma(Metz et al., 2019).

### **Opiates**

Opioid analgesics, such as Morphine, Fentanyl and Pethidine immediately after the traumatic events have shown to be beneficial in reducing the development and severity of acute stress reaction to the trauma(Saxe et al., 2001; Bryant et al., 2009; Holbrook et al., 2010; Hong et al., 2016). It may possibly have limited fear conditioning and the consolidation of traumatic memory in the aftermath of trauma.

### **Others**

- Prazosin, an alpha-1 selective adrenergic blocker, as a monotherapy or in adjunct to SRIs, is effective for sleep disturbance (insomnia and nightmares). Monitor for hypotension before and after its administration. (Reist et al., 2020)
- Anecdotal evidence for lamotrigine and/or gabapentin in the treatment of nightmares and flashbacks (Kishimoto et al., 2014)

- ECT is effective when patients have concurrent severe depression and/or suicidality (Kellner & Romanella, 2019)

## CONCLUSIONS

Over the past three decades, stress-related disorders have gained importance resulting in having a separate diagnosis of “Acute stress disorder” in DSM – IV (TR) to a separate grouping category “Trauma- and stress- related disorders” in DSM-5. The prevalence of ASD is variable and largely dependent on nature of trauma and the individuals who experienced the trauma. Given the fact that the experience of acute stress reaction following a traumatic event is not so uncommon, there is debate on adding a “pathological disorder” label to it. Nonetheless, it is crucial to recognize ASR and intervene as early as possible to reduce the long-term morbidity. There is need to have more systematic studies in ASD to establish evidence for the prevalence, identifying the biomarkers of vulnerability and resilience to stress, examining the effectiveness of interventions in preventing its morbidity and long term sequelae.

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## **STRESS AND POST-TRAUMATIC STRESS DISORDER**

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## **INTRODUCTION**

The effect of extreme degree of stress on human beings is well known and has been described in various forms from literature to scientific writings. Some examples include: shell shock, battle fatigue, combat neurosis, soldier's heart, etc. based on the presentations following wars. Beside wars, there are many severe traumatic experiences e.g. fire, accidents, natural disasters, which lead to intense mental health consequences. These observations have been the building blocks for the syndrome 'Post Traumatic Stress Disorder' (PTSD) which was coined first time in DSM-III (American Psychiatric Association, 1980). In DSM-I there were categories titled, 'Gross stress reaction' and in DSM-II 'Transitional Situational Disturbance' (adjustment reaction) (Tomb, 1994). Gradually, the evidence base has grown secondary to burgeoning research in this area. The diagnostic criteria for

PTSD have undergone refinements, prevalence has been studied extensively and efficacy of many interventions has been tested. Considering ubiquitous nature of stress and its effects, expanding concept and relevance of PTSD, this area deserves a detailed study.

## **NATURE OF STRESS AND PTSD**

PTSD is one of the few psychiatric disorders which are clearly associated with a cause. Concepts describing the nature of the precipitant stresses have undergone changes over the years. The stresses that have been usually associated with PTSD have been wars, catastrophic disasters, rape, torture, experience of terrorism etc. However, gradually a large number of different types of stressors have been associated with PTSD (Box 1). Examples of stresses where PTSD have been diagnosed included are traffic accidents, acute and chronic medical illnesses e.g. myocardial infarction, burns, admission to intensive care unit, etc., exposure to community stress, job stress, exposure to those who have been traumatised, and even exposure to the awareness that others have been traumatised have been reported to be associated with PTSD (Tomb, 1994). In this context it is interesting to review the stressor criterion in the diagnostic systems.

### **Box 1. Examples of stress associated with PTSD**

- Childhood sexual or physical abuse
- Genocide campaigns
- Industrial accidents: explosions
- Mass shooting
- Motor vehicle, train, plane, ferry accidents
- Natural disasters: earthquake, cyclone, flood, fire
- Prolonged domestic violence
- Rape
- Slavery
- Terrorism
- Torture
- War

The list is not exhaustive.

Nature of stress that is considered to be associated with PTSD has changed over time in the diagnostic classifications. It was described as ‘severe combat or civilian catastrophe’ in DSM-I; which was changed to ‘a psychologically

distressing event outside the range of usual human experience' in DSM-III and with a further qualification that 'would be markedly distressing to almost anyone' in DSM-III-R. In DSM-IV, the concept was broadened to include a response of 'intense fear, helplessness, or horror' to the stressor criterion, which was 'person has experienced, witnessed or been confronted with an event or events that involved actual or threatened death or serious injury or a threat to the physical integrity of oneself or others'. The focus shifted from the severity of the traumatic event to both trauma and individual's response to it. The latter part suggests the vulnerability factor of the individual. In effect, concept of PTSD expanded considerably, e.g. people who experienced relatively not so severe trauma but had extreme reactions, and those who had indirect exposure to trauma to others could also be considered to have PTSD if other criteria were fulfilled. The dilution of stressor criterion resulted in the overinclusion and increased prevalence of PTSD.

In DSM-5 (American Psychiatric Association, 2013), the stressor criterion has been described as 'exposure to actual or threatened death, serious injury or sexual violation in one or more of the following ways: i. directly experiencing the traumatic event; ii. witnessing, in person, the event(s) as they occurred to others; iii. learning that the event(s) occurred to a close family member or close friend (in case of actual death or a family member or friend, the event(s) must have been violent or accidental); and iv. experiencing repeated or extreme exposure to aversive details of the traumatic event(s). The exposure does not apply to exposure through electronic media, television, movies or pictures unless this exposure is work-related. Subjective reaction (intense fear, helplessness or horror) criterion has been eliminated. This way, stressor criterion in DSM-5 is more focused and has better clarity (American Psychiatric Association, 2013). In ICD10, the nature of stress is mentioned as 'a stressful event or situation (either short- or long-lasting) of exceptionally threatening or catastrophic nature, which would be likely to cause pervasive distress in almost anyone' (World Health Organization, 1992). The description of stress in the PTSD diagnosis in ICD-11 is 'extremely threatening or horrific event or series of events.' It is evident from these descriptions that the stress associated with PTSD is conceptualised at the higher degree of severity.

## **PREVALENCE**

Reported figures of prevalence of PTSD vary widely, secondary to factors such as severity of trauma, its meaning for the affected individual, degree of loss etc. It is understandable that following extreme trauma such as violent rape and life-

threatening combat situation, considerable proportions of individual experience PTSD. Estimated lifetime prevalence of PTSD was 7.8% in National comorbidity survey (Kessler et al., 1995), whereas lifetime prevalence in vulnerable war veterans have been reported from 30% to almost 90% in most brutalised prisoners of war (Tomb, 1994)..

Community prevalence has been usually in the range of 1-3%; however there are elevated rate of around 9.2% in communities with higher incidence of traumatic events (Tomb, 1994) (M. B. Stein et al., 1997). In one study, experience of traumatic events was reported by 26% men and 17.7% women, but the PTSD prevalence was 1% and 2.2% respectively (Perkonigg et al., 2000).

Following natural disasters reported figures range from as low as 4.5-9% (Caldera et al., 2001) to 95% after Armenia earthquake (Goenjian et al., 1995). Examples of reported figures of PTSD prevalence following some major disasters are as follows: Hurricane Hugo 5% in children (Shannon et al., 1994); Northridge earthquake 28.5% (Asarnow et al., 1999), hurricane Andrew 36% (David et al., 1996), supercyclone 44.3% in adults (Kar et al., 2004) and 26.9% in adolescents (Kar & Bastia, 2006), Northridge earthquake 13% (McMillen et al., 2000); Latur earthquake 23% (Sharan et al., 1996), Oklahoma City bombing 34.3% (North et al., 1999), mass shooting 28% in acute phase, 24% at follow-up (North et al., 1997); shipyard explosion, Denmark 41% (Elkliit, 1997) and 2004 tsunami in India 70.9% (Kar et al., 2014). Besides trauma related factors and individual and community vulnerability, methodological differences in the studies contribute to the variations in reported prevalence.

## AETIOLOGY

Not all individuals who have traumatic experience develop psychiatric disorder. In only a proportion of exposed people stress related mental illnesses are observed which can be of various kinds, one of which is PTSD. This suggests that there are clearly other factors besides trauma operating in the pathogenesis. There are various risk factors reported from the studies. Acute stress reactions with biological and psychological changes, dissociative reactions may indicate severity of stressor and its impact on the individual. Peri-traumatic dissociation is an indicator for possible development of PTSD. It has been suggested that pre-existing anxiety disorders increases the vulnerability for PTSD. This has an impact on severity, chronicity and outcome as well. Some of the risk and vulnerability factors are given in box 3.

**Box 3. Risk and vulnerability factors**

Demographic factors	<ul style="list-style-type: none"> <li>• Females</li> <li>• Children</li> <li>• Illiteracy / lower educational level</li> <li>• Middle socioeconomic status</li> <li>• Financial problem</li> </ul>
Individual factors	<ul style="list-style-type: none"> <li>• Level of trait anxiety</li> <li>• Neuroticism</li> <li>• Introversion</li> <li>• Limited coping abilities</li> <li>• More frequent use of cognitive and avoidance coping strategies</li> <li>• Low intelligence</li> <li>• Genetic predisposition to poor stress tolerance</li> </ul>
Clinical factors	<ul style="list-style-type: none"> <li>• History of mood disorder</li> <li>• History of anxiety disorder</li> <li>• Depression</li> <li>• Personality disorder, particularly antisocial and narcissistic</li> <li>• Peri-traumatic dissociation</li> <li>• Acute stress reaction</li> </ul>
Pre-trauma factors	<ul style="list-style-type: none"> <li>• History of psychiatric problems</li> <li>• Pre-trauma anxiety disorder</li> <li>• Family psychiatric history</li> <li>• History of trauma</li> <li>• Limited social support</li> </ul>
Trauma factors	<ul style="list-style-type: none"> <li>• Perceived stress</li> <li>• Fear of death</li> <li>• Displacement</li> <li>• Dose of exposure</li> <li>• Injury</li> <li>• Life-threatening trauma</li> <li>• Loss of property / resource</li> <li>• Loss of relatives</li> <li>• Damage to livelihood</li> </ul>
Post-trauma factors	<ul style="list-style-type: none"> <li>• Inadequate support,</li> <li>• No or inadequate intervention</li> </ul>

(Asarnow et al., 1999); (Brady et al., 2000); (Caldera et al., 2001); (Elklit, 1997); (Griffin et al., 1997); (Kar et al., 2007); (Kar et al., 2014); (Lonigan et al., 1994); (McMillen et al., 2000); (North et al., 1999); (Tomb, 1994); (Sharma & Kar, 2018)

### Biology of Ptsd

Biological vulnerability is a potential contributor considering wealth of evidence suggesting the effect of stress on various systems. The information on the biological substrates or contributing factors is diverse and the literature suggests that psychophysiological, neuroanatomical, endocrine-immunological, genetic, and epigenetic factors play an important role (Noll-Hussong, 2014).

There are many studies that indicate a probable differentiation of patients with PTSD compared to other anxiety disorders or normal individuals. There is an increased risk of PTSD with a family history of psychiatric disorder (Koenen et al., 2002). Monozygotic twins have significantly higher concordance for PTSD than dizygotic twins (Cornelis et al., 2010). Genetic contribution to the pathogenesis of PTSD has been proposed with a heritability of about 30-35% (Domschke, 2012).

Heightened autonomic nervous system arousal when exposed to the cues of the original trauma has been reported in PTSD patients (Sutherland & Davidson, 1994) (Kobayashi et al., 2014). Higher autonomic reactivity in PTSD indicates an acquired general sensitization of the nervous system (Noll-Hussong, 2014).

Corticotrophin-Releasing-Factor and Hypothalamic-Pituitary-Adrenal Axis system are known to be implicated in stress response. In PTSD patients higher cortisol levels have been significantly related to higher levels of numbing symptoms in one study (Stoppelbein & Greening, 2015).

Current research is emphasizing on pathogenic biomarkers, molecular networks and other biological substrates for PTSD. These initiatives may help in identifying people with specific vulnerabilities and guiding treatment approaches.

### CLINICAL FEATURES

PTSD has been described as a heterogeneous disorder which can present in different symptom clusters. It has symptomatic overlaps with depressive and anxiety disorders which may make the diagnostic process complex. Usual symptom clusters of PTSD include persistent remembering of the trauma in various ways, avoidance, increased psychological sensitivity and arousal, and associated alterations in mood and cognitions.

### **Persistent reliving of the trauma**

Patients report vivid memories of the trauma, which recur repeatedly. Patients relive the experience with intrusive and distressing thoughts and perceptions in the form of ‘flashbacks’, daytime imagery, illusions or nightmares. In children repetitive play with trauma related themes are observed. During these periods of re-experience there may be intense physiological reactions.

### **Avoidance**

There is fear and avoidance of the internal or external cues that may remind the trauma. There is actual or preferred avoidance of activities, people, place and situations reminiscent of the traumatic event. Along with this there is distress when exposed to the circumstances resembling or associated with the traumatic experience.

### **Alterations in mood and cognition**

Usual mood states include anxiety, depression and irritability along with related cognitions. Trauma - related negative emotions (e.g., fear, horror, anger, guilt, or shame) are persistently reported along with lack of ability to experience positive emotions. Occasionally there may be sudden dramatic outbursts of fear, panic and aggression, triggered by stimuli arousing a sudden recollection and/or re-enactment of the trauma or of the original reaction to it (World Health Organization, 1992).

There is a sense of numbness, emotional blunting, detachment, unresponsiveness to surroundings and anhedonia which are observed commonly. Patients express inability to remember some important and specific aspects of the traumatic experience either partially or completely (World Health Organization, 1992). There may be distorted cognitions such as blame of self or others about contributing the event or about its consequences, and negative beliefs and expectations about oneself or the world. It may include ideas like: “There’s danger lurking everywhere”, “I can’t trust anyone”, “I’ll never get over it”, etc. (Frommberger et al., 2014).

### **Alterations in arousal and reactivity**

There is usually autonomic hyper-arousal with hypervigilance and startle reactions. In addition, difficulty in concentration is usually reported. Most patients suffer from insomnia. There may be aggressive, self-destructive or reckless behaviour.

### **Other associated symptoms**

Besides above symptoms many PTSD patients may have dissociative symptoms such as depersonalisation and derealisation. In depersonalisation the person feels detached from self, observes self as an outsider or feels as if being in a dream. In derealisation, the outside feels unreal and distorted. Suicidal ideas and attempts are known to be associated with catastrophic stress (Kar, 2010); and has been reported to be highly prevalent in PTSD patients (Tarrier & Gregg, 2004). Anxiety and depressive symptoms are common concomitant of PTSD, which might be at a syndromal level in a proportion of patients (Kar & Bastia, 2006). Excessive use of drugs and alcohol are also observed.

Psychotic-like experiences have been described in severe PTSD; however, there are controversies about the nature of these experiences. While psychotic features in PTSD has been reported in a range of 15-64% (Gaudiano & Zimmerman, 2010), some opine that these may not be psychotic experiences (Lindley et al., 2014). There is a debate about having a psychotic subtype of PTSD (Bosson et al., 2011) (Gaudiano & Zimmerman, 2010). Interestingly, there are people who have PTSD while recovering from a psychotic illness (Brady et al., 2000), serious physical illness or admission to Intensive Care Unit (Tripathy et al., 2020).

### **Subsyndromal PTSD**

It has been observed that many traumatised individuals suffer from a sub-syndromal form of PTSD. They do not present with all the criteria for the diagnosis (McMillen et al., 2000). These individuals with partial PTSD have functional impairment and need clinical attention. In a community survey estimated prevalence of partial PTSD was 3.4% for women and 0.3% for men in contrast to 2.7% and 1.2% for full PTSD respectively (Stein et al., 1997). In situations where catastrophic traumas affect large population e.g. following natural disasters the proportions of subsyndromal PTSD have been observed to be high (Kar et al., 2007).

## **COURSE**

There is a temporal relationship between the trauma and PTSD. Following the traumatic experience onset of PTSD may be observed after a latency period ranging few weeks to months, although in proportion of cases it may be after 6 months (delayed onset). However, most people may have stress symptoms soon after the event.

Recovery is expected in majority of PTSD cases. Symptoms may return or exacerbate if the person experiences new trauma, even if the second trauma is less severe than the first. Course of PTSD is usually fluctuating, and it appears from various studies that PTSD may last long-term. In a proportion of approximately 20% to 30% of patients PTSD becomes chronic and continues for years (Frommberger et al., 2014). There may be a transition to enduring personality change (World Health Organization, 1992) in some patients.

Symptoms of PTSD may fade over time and after sometime the proportion of people continuing to have syndromal PTSD dwindle. For example, incidence of PTSD after a rape or violent assault may be around 50% within a month or two, but after several months to 1 year it is around 25 to 30%, and after several years it may lie in 5-10% range (Cohen, 1980). However in around one third of PTSD patients the symptoms do not remit even after 6 or more years regardless of treatment (Kessler et al., 1995). In the presence of comorbidities, the duration until remission of PTSD is longer (Brady et al., 2000).

Post-trauma factors influence in development, progress and outcome of PTSD. Following a traumatic experience, the way affected individuals are treated may have a major influence. Adequate and timely support may guard against PTSD, shorten the course (Tomb, 1994) and may lead to a favourable prognosis.

## **ASSESSMENT**

Clinical assessment involving detailed history taking and mental state examination is the key in the diagnostic process. In-depth exploration or inquiry of the trauma may be distressing for many individuals if it is attempted in first meeting; it should be preferably differed until the patient is more comfortable to discuss that. Initial interaction with the patients should be highly supportive, providing feelings of safety and reassurance.

Cultural sensitivity is extremely important in assessment and management of PTSD patients. Meaning of trauma for the individual and community, their approach to help-seeking, hesitations in seeking professional help, and the prevalent stigma should be considered. Communication through the language spoken by the patient, and therapists from the same culture may be better.

There are many scales to support clinical assessment of PTSD in various scenarios and needs. Some of them are given in box 2. These may help in evaluating various symptoms and the severity.

**Box 2. Examples of Scales for PTSD**

Child PTSD Symptom Scale for DSM-5 (CPSS-5)	(Edna B. Foa et al., 2018)
Clinician Administered PTSD Scale (CAPS)	(Blake et al., 1995)
Davidson Trauma Scale (DTS)	(J. R. T. Davidson et al., 1997)
Impact of Events Scale (IES)	(Horowitz et al., 1979)
Impact of Events Scale-Revised (IES-R)	(Weiss & Marmer, 1997)
Los Angeles Symptom Checklist	(King et al., 1995)
Mississippi Scale for Combat-Related PTSD (M-PTSD)	(Keane et al., 1988)
Peritraumatic Dissociation Experiences Questionnaire	(Marmar et al., 1994)
Peritraumatic dissociation index	(Griffin et al., 1997)
Posttraumatic Diagnostic Scale	(Edna B. Foa et al., 1997)
Post-traumatic Stress Disorder-Interview (PTSD-I)	(J. Davidson et al., 1990)
PTSD Check List - Civilian Version (PCL-C)	(Weathers et al., 1994)
PTSD checklist (PCL)	(Blanchard et al., 1996)
PTSD Checklist for DSM-5 (PCL-5)	(Weathers et al., 2013)
PTSD Symptom Scale (PSS)	(Edna B. Foa et al., 1993)
Self-Rating Inventory for PTSD	(Hovens et al., 1994)
Self-Rating Scale for PTSD (SRS-PTSD)	(Carlier et al., 1998)
Brief Trauma Questionnaire (BTQ)	(Schnurr et al., 2002)
The Primary Care PTSD Screen for DSM-5 (PC-PTSD-5)	(National Center for PTSD, 2013; Prins et al., 2016)
Posttraumatic Diagnostic Scale for DSM-5 (PDS-5)	(Edna B. Foa et al., 2016)
Primary Care PTSD Screen (PC-PTSD)	(Prins et al., 2004)
Short Form of the PTSD Checklist-Civilian Version	(Lang & Stein, 2005)
Short Post-Traumatic Stress Disorder Rating Interview	(Connor & Davidson, 2001)
Trauma Screening Questionnaire	(Brewin et al., 2002)

*List is not exhaustive*

## ASSESSMENT OF PTSD AND MEDICOLEGAL IMPLICATIONS

An area of emerging importance in the assessment of PTSD is related to compensation claims secondary to PTSD related disability. With ever increasing situations like war, terrorism, industrial accidents, many people exposed to these are reporting with PTSD symptoms. The compensation claims have increased in recent years and many factors including increased prevalence, delayed onset, symptomatic overlap with other disorders, malingering and economic issues have been considered (McNally & Frueh, 2013) (Ahmadi et al., 2013). PTSD malingering is estimated to occur in at least 20% of compensation-seeking combat veterans (Ahmadi et al., 2013). As the confusion regarding what constitutes a traumatic stressor, difficulties with differential diagnosis and comorbidities, ease in malingering, dependence on subjective report and improper linking of symptoms to causes of behaviour continue, along with the increased scope of claim, the legal implications of the process of assessment and diagnosis of PTSD cannot be over-emphasized (Zoellner et al., 2013)(Levin et al., 2014).

Identification of malingering needs realisation of its existence and careful clinical assessment. Techniques like using open ended questions, taking detailed history of premorbid functioning, course of symptoms, collateral history, being objective, looking for signs of hypervigilance, concentration deficits, irritability and avoidance during assessment may help. Some characteristics may suggest possibility of malingering e.g. the initial clinical assessment in a medico legal context, discrepancy in claimed stressor, symptomatic presentation, disability and observational findings, lack of cooperation in assessment or treatment adherence and antisocial personality disorder. Malingeringers often have histories of behavioural issues in school, workplace, military; sporadic employment and attendance at work; substance use, financial issues and legal problems (Ali et al., 2015). Assessment may be added by specific instruments for example Personality Assessment Inventory Malingering Index, Negative Distortion Scale (Wooley & Rogers, 2014) and Miller Forensic Assessment of Symptoms Test (M-FAST) (Ahmadi et al., 2013). However the assessments based on instruments have their own shortcomings as well (Kleinman & Martell, 2015). Physiologic testing for PTSD e.g. script-driven mental imagery or sudden loud tones which is usually used in research settings may be helpful; however, they cannot be sole determinant of malingering. It is suggested that if malingering is suspected multiple methods of

enquiry are recommended (Ali et al., 2015). In summary, assessments in this kind of possible scenarios are complex and can be clinically challenging.

## DIAGNOSIS

Criteria for diagnosis of PTSD are very detailed in DSM and ICD classificatory systems and cover the core areas of intrusion, hyperarousal and avoidance. PTSD was usually described under 3 major symptom clusters: re-experiencing, avoidance/numbing, and arousal which was maintained in DSM-IV (American Psychiatric Association, 1994); however this has been changed in DSM-5 (American Psychiatric Association, 2013) to 4 clusters: intrusion, avoidance, negative alterations in cognition and mood, and alteration in arousal and reactivity.

Duration criterion for diagnosis in DSM-5 is one month. In DSM-5, PTSD has become developmentally sensitive with lower diagnostic thresholds for children and adolescents. There is a subtype for children age 6 years or younger with this disorder. It can be further specified if it is associated with dissociative symptoms such as depersonalisation and derealisation; and whether there is delayed expression if the full criteria are not met until 6 months after event (American Psychiatric Association, 2013).

There are major changes of diagnosis of PTSD in ICD-11, which is now grouped in the Disorders Specifically Associated with Stress. It has three features e.g. re-experiencing the traumatic event in the present; deliberate avoidance of reminders likely to produce re-experiencing; and persistent perceptions of heightened current threat, which should be present in all cases and cause significant impairment. Re-experiencing the cognitive, affective or physiological aspects of the trauma are required here and now rather than just remembering the event.

ICD-11 has introduced Complex PTSD (World Health Organization, 2020). It is observed usually after severe and prolonged stressors, multiple or repeated traumatic events from which escape is difficult or impossible (Reed et al., 2019). Besides all the diagnostic requirements for PTSD, complex PTSD has additional features such as severe and persistent (i) problems in affect regulation; (ii) beliefs about oneself as diminished, defeated or worthless, accompanied by feelings of shame, guilt or failure related to the traumatic event; and (iii) difficulties in sustaining relationships and in feeling close to others. Significant impairment in personal, family, social, educational, occupational or other important areas of

functioning by the symptoms is an essential criterion (World Health Organization, 2020). Complex PTSD replaces the ICD-10 diagnosis of enduring personality change after catastrophic experience.

There are considerable changes in the diagnostic criteria for PTSD in recent revisions of diagnostic classifications. It is expected that the ICD-11 criteria of PTSD will increase the diagnostic threshold compared to ICD-10 (Kar & Sharma, 2020; Reed et al., 2019) and make the PTSD diagnosis more homogenous.

## **DIFFERENTIAL DIAGNOSIS**

Common differential diagnoses include mood and anxiety disorders especially stress-induced exacerbations of already existing mood or anxiety disorders. Acute stress reactions can be distinguished based on the time duration as these are normal reactions to stress and subside after a time course; and it is no more considered as a mental illness in the ICD-11. Adjustment disorders are distinguished by different pattern of symptoms and cover a wide variety of stresses which are not catastrophic in nature. Many people may develop acute psychosis following traumatic experiences, where diagnoses like brief reactive psychoses, brief psychotic disorders or acute and transient psychotic disorders are considered. Enduring personality change secondary to the extreme traumatic experience which was separate diagnosis to PTSD, is considered as Complex PTSD in ICD-11.

## **COMORBIDITY**

Comorbidity with other psychiatric disorders is common in PTSD. A considerable proportion of PTSD patients have other diagnoses which are commonly depression, anxiety and substance use disorders (Kar & Bastia, 2006)(Brady et al., 2000). Comorbidity with panic disorder, social phobia and dissociative disorders with PTSD has been reported. Trauma, PTSD and dissociative amnesia are linked. Comorbidity with somatization disorder, borderline personality disorder, drug dependency, psychosis, dissociative identity disorder (Frommberger et al., 2014); psychotic illness (de Bont et al., 2013), even schizophrenia (Jones & Steel, 2014) (Steel et al., 2011) has been reported.

## **MANAGEMENT OF PTSD**

Mainstay of management of PTSD is psychological, however there are definite role of pharmacotherapy. The intervention should be individualised depending upon

the need; and involve support from families and community when appropriate considering the nature of the trauma. Interventions may start soon after the experience of the trauma and may need to be continued long term depending upon response.

In the immediate aftermath of significant trauma, practical support and help are instrumental in beginning the process of recovery. In general, informing about the post-traumatic stress reactions and reassuring that these are common following extremely traumatic events may help. Re-establishing contact with families, taking care of physical needs and communicating with the victims to instil sense of reality are needed.

Support for families is important which can include information, psycho-education, reassurance and practical support. These can go a long way in creating a therapeutic environment around the affected individual. This helps decreasing the bewilderment and confusion which are common after traumas affecting masses.

If the symptoms are mild and are present for less than one month, active monitoring may be considered, with a follow up at one month (NICE, 2018). A screening instrument may be used after around a month of the traumatic experience as an aid for clinical assessment (Box 2). However, if the symptoms are moderate to severe or are associated with other comorbidities and risks, psychological and pharmacological interventions should be started. Treatment of comorbidities is extremely important and the management plan should be complementary for both PTSD and the comorbid conditions. This may lead to faster resolutions of symptoms. In addition, self-harm or suicidal risk, if associated, needs to be attended as priority.

### **Psychological Interventions**

Different types of psychological interventions have been studied for PTSD. These mainly include Cognitive Behaviour Therapies such as Trauma-Focused Cognitive Behaviour Therapy (TF-CBT), cognitive processing therapy (CPT) and prolonged exposure (PE) therapy; eye movement and desensitisation reprocessing (EMDR), anxiety management programmes, and relaxation based therapies. However many other approaches such as imagery re-scripting and reprocessing therapy (IRRT), narrative exposure therapy (NET), brief eclectic psychotherapy (BEP), psychodynamic therapy, hypnotherapy, biofeedback-assisted desensitization, etc.

have also been tried (Kar, 2011a; Lancaster et al., 2016; NICE, 2018; Watkins et al., 2018) (Frommberger et al., 2014). WHO recommends individual or group TF-CBT, EMDR or stress management for adults (Tol et al., 2014). In general, trauma-focused interventions seem to be most effective (Coventry et al., 2020). Some meta-analysis report greater benefit of psychotherapeutic treatments than pharmacological treatments (Merz et al., 2019).

There are controversies about usefulness of debriefing. Practice of brief, single-session interventions (debriefing) alone is discouraged (NICE, 2005). Routine use of non-trauma-focused interventions such as relaxation or non-directive therapy is also not recommended. There is no convincing evidence for supportive therapy/non-directive therapy, hypnotherapy, psychodynamic therapy or systemic psychotherapy (NICE, 2005).

### **Cognitive behaviour therapy**

CBT has been well researched as an intervention for PTSD. There is substantial body of evidence suggesting that TF-CBT is an effective for both acute and chronic PTSD in adults, children and adolescents (Kar, 2011a). CBT for PTSD usually entail education about common reactions to trauma, relaxation training, identification and modification of cognitive distortions. In addition, there are many specific elements used in this context. Some of these are imaginal reliving of the trauma memory, imaginal exposure, in vivo exposure, facilitation of posttraumatic growth (Maercker et al., 2006); stress inoculation and graduated exposure to avoided situations and trauma re-experiences (Williams et al., 2003); exposure to trauma reminders, cognitive restructuring, re-scripting or imagery re-scripting etc. (Sijbrandij et al., 2007) (Kindt et al., 2007).

CBT for PTSD is usually delivered in weekly or biweekly sessions (Sijbrandij et al., 2007). However, recently an intensive version of Cognitive Therapy for PTSD (CT-PTSD) has been attempted where patients received up to 18 hours of therapy over a period of 5 to 7 working days, followed by 1 session a week later and up to 3 follow-up sessions. The results suggested that intensive CT-PTSD was a feasible and promising alternative to weekly treatment. However this warrants further evaluation in randomized trials (Ehlers et al., 2010).

TF-CBT can be provided one-to-one and group sessions (Beck & Coffey, 2005), in various settings which included community centres, primary care clinics

and hospitals depending upon the context of the traumatic event. Provision of CBT through the internet is also a viable option (Knaevelsrud & Maercker, 2007). Online treatment of PTSD patients with therapist support by e-mail only has also been reported. CBT has been used across cultures successfully; however it may need to be adapted for cultural and local sensitivities (Udomratn, 2008).

### **Cognitive Processing Therapy**

CPT is a trauma focused therapy based on social cognition and emotional processing theory. It is assumed that trauma is integrated to existing schema by assimilation, accommodation and over-accommodation, leading to cognitive distortions about themselves, world and others. Primary objective of CPT is shifting beliefs to accommodation. It is conducted in 12 weekly sessions in one-to-one or group sessions (Watkins et al., 2018).

### **Prolonged Exposure**

PE has been a recommended treatment of PTSD. Based on emotional processing theory which suggests that fear is represented in memory as a cognitive structure that includes feared stimuli, responses and associated meaning. Sometimes this structure becomes abnormal with unrealistic threat representation, excessive response. PE focuses on altering the dysfunctional fear structure. It is done in around 8-15 sessions which includes psychoeducation, breathing retraining, in vivo and imaginal exposure (Watkins et al., 2018).

### **Eye movement and desensitisation reprocessing**

Methods of EMDR consist of visualizing the trauma while making eye movements by tracking rapid side-to-side movement of the therapist's finger. It is a form of exposure, along with components from other modalities of psychotherapeutic intervention such as relaxation and cognitive therapy (E. B. Foa, 2000). It has been reported that both EMDR and trauma-focused CBT are equally efficacious in PTSD (Seidler & Wagner, 2006). EMDR has also been effective for associated sleep and psychological symptoms (Raboni et al., 2014).

### **Pharmacological Interventions**

The evidence base of pharmacological treatment of PTSD is expanding. There are beneficial effects for various medications such as paroxetine, sertraline, venlafaxine, mirtazapine, amitriptyline and phenelzine (Box 4). However these are often recommended along with or as a second line intervention following a

trauma-focused psychological treatment considering the limitations in the reported studies (Hoskins et al., 2015). WHO guidelines emphasize that selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants should not be considered as first line (Tol et al., 2014). A recent meta-analysis found fluoxetine, paroxetine and venlafaxine as potential medications although effect size was small (Hoskins et al., 2015). Anyway, sertraline and paroxetine have FDA support for PTSD (Lancaster et al., 2016) and are licensed in the UK; venlafaxine is also recommended for PTSD (NICE, 2018). If the drug treatment is effective it should be continued for at least a period of 12 months (NICE, 2005).

**Box 4: Summary of current evidence on pharmacotherapy of PTSD**

Method	Medications reported to be beneficial
<b>Systematic review and meta-analysis</b> (Hoskins et al., 2015)	<ul style="list-style-type: none"> <li>Fluoxetine, paroxetine and venlafaxine</li> </ul>
<b>Network meta-analysis</b> (de Moraes Costa et al., 2020)	<ul style="list-style-type: none"> <li>Topiramate, risperidone, quetiapine, paroxetine, venlafaxine, fluoxetine, and sertraline - possible first-line alternatives</li> <li>Fluoxetine, lamotrigine, and phenelzine better than placebo for acceptability</li> <li>Fluoxetine – first line balancing efficacy and acceptability</li> </ul>
<b>Systematic review and meta-analysis</b> (Astill Wright et al., 2019)	<ul style="list-style-type: none"> <li>Hydrocortisone - emerging possibility for the prevention of PTSD within three months after trauma for those with severe physical illness or injury. More studies needed, currently not recommended for routine use.</li> <li>No significant effects for propranolol, oxytocin, gabapentin, fish oil, dexamethasone, escitalopram, imipramine and chloral hydrate.</li> </ul>
<b>Review</b> (Murray B. Stein, 2019)	<ul style="list-style-type: none"> <li>SSRIs e.g. sertraline and paroxetine, venlafaxine.</li> <li>SGA e.g. risperidone, quetiapine as monotherapy or augmentation, some evidence.</li> <li>Prazosin (Alpha-adrenergic receptor blocker)</li> <li>Insufficient evidence of effectiveness of antidepressants other than SSRI/SNRIs</li> </ul>

Method	Medications reported to be beneficial
<b>Network meta-analysis</b> (Cipriani et al., 2018)	<ul style="list-style-type: none"> <li>Desipramine, fluoxetine, paroxetine, phenelzine, risperidone, sertraline, and venlafaxine - more effective than placebo.</li> <li>Phenelzine better than other, only drug significantly better than placebo in terms of dropouts, data not robust enough to suggest as a drug of choice.</li> <li>Mirtazapine relatively high for efficacy, but not for acceptability</li> </ul>
<b>Systematic review and component network meta-analysis</b> (Coventry et al., 2020)	<ul style="list-style-type: none"> <li>Antipsychotics and prazosin - effective in reducing PTSD symptoms.</li> </ul>
<b>Systematic Review and Meta-Analysis</b> (Huang et al., 2020)	<ul style="list-style-type: none"> <li>Medications are superior to placebo; SSRIs and atypical antipsychotics have significant efficacy compared with placebo in severe or extremely severe PTSD.</li> <li>Only atypical antipsychotics have superior efficacy than placebo in veterans.</li> </ul>
<b>Systematic meta-analysis</b> (Ipser & Stein, 2012)	<ul style="list-style-type: none"> <li>Short- and long-term efficacy exists for SSRIs, promising findings for the SNRI venlafaxine and risperidone.</li> <li>Prazosin and the atypical antipsychotics have some efficacy in treatment-resistant PTSD</li> </ul>

SSRI: selective serotonin reuptake inhibitors; SNRI: selective noradrenergic reuptake inhibitor; SGA: Second Generation Antipsychotics

Medications are helpful for associated symptoms like insomnia, in which case short term hypnotics may be given. Agents with potential are trazadone for sedative effects and prazosin for sleep and nightmares (Lancaster et al., 2016). Antipsychotics such as risperidone can be considered if there are disabling symptoms e.g. severe hyperarousal or psychotic symptoms, or if the symptoms do not respond to other drug or psychological treatment (NICE, 2018). In addition, medications should be given for associated comorbid diagnoses when indicated. There is suggestion for pharmacologically-augmented psychotherapy as an improved approach for anxiety and trauma related disorders and the role of cognitive enhancers in this regard are being explored (Singewald et al., 2015).

### **Management in Children and Adolescents**

Management of PTSD in children and adolescents is still evolving. A range of interventions have been tried e.g. CBT, trauma-counselling, brief trauma/grief focused therapy, group therapy, play and art therapies (Kar, 2009). NICE recommends individual trauma-focused CBT (age 5-17) for prevention and treatment of PTSD, and EMDR for treatment (age 7-17) and does not recommend drug treatment (NICE, 2018). However, apart from trauma-focused psychological interventions, there is at present no good evidence for the efficacy of play therapy, art therapy or family therapy (NICE, 2005). WHO recommends individual or group TF-CBT or EMDR; and does not suggest antidepressants for children and adolescents (Tol et al., 2014). NICE does not recommend drug treatment for children or young people under 18 for PTSD (NICE, 2018).

TF-CBT for children and adolescents should be adapted to their age, circumstances and developmental stage (NICE, 2005). It is a validated strategy for PTSD in children and adolescents particularly when associated with anxiety and mood disorders (Kar, 2011b). Cognitive behavior interventions in older children have included direct discussion of the trauma, desensitization and relaxation techniques and cognitive reframing. Contingency reinforcement programs for problematic behaviors have been suggested to be useful. CBT has been provided in groups following disasters with many PTSD patients. It is important to involve parents and families in the PTSD treatment programmes for children and adolescents (Kar, 2009); but parents-only programmes are unlikely to benefit (NICE, 2005).

### **MANAGEMENT OF COMPLEX PTSD**

Persons with complex PTSD will have additional needs. While the general management will in the line of PTSD, they may need extra time, a greater number of sessions, attention to other associated stressors, risk issues, etc. Factors that may be barriers to successful interventions or engagement e.g. substance use, dissociation, emotional dysregulation, interpersonal issues need to be addressed first. They may also need continued support to deal with residual PTSD symptoms or comorbidities (NICE, 2018).

### **PREVENTION OF PTSD**

As the aetiology of the presence of a traumatic event is clearly identified and many individual vulnerability factors are known; it seems plausible to institute appropriate measures to prevent the development of PTSD. Considering the

importance of preventability, however there are only a few studies. According to a systematic review, multiple session interventions aimed at all individuals exposed to traumatic events should not be used (Roberts et al., 2009). Another systematic review on psychological debriefing suggests that it does not prevent PTSD (Rose et al., 2002) and its use is not recommended (Rose et al., 2002)(NICE, 2018). In addition, there is no robust evidence base to reflect on primary prevention of PTSD (Skeffington et al., 2013).

Recent NICE guideline suggests therapies with preventive role in adults. If the affected individual has clinically important symptoms of PTSD and have been exposed to 1 or more traumatic events in the previous month cognitive therapy for PTSD, CPT, NET and PE therapies may be considered (NICE, 2018). There are many attempts to study if pharmacological intervention to the traumatised persons can prevent PTSD. Various medications have been tried including propranolol, escitalopram, temazepam and gabapentin. However there is no adequate evidence to support their use (Amos et al., 2014)(Suliman et al., 2015). Interestingly there is some emerging evidence for hydrocortisone for the prevention of PTSD development in adults (Amos et al., 2014) (Zohar et al., 2011). Considering the limitations of the current studies further research is needed in this area.

## **CONCLUSIONS**

PTSD is common in population and its prevalence increases considerably following extreme trauma affecting masses. Most of the people affected by the catastrophic events experience stress symptoms; however only a proportion develops PTSD. Practical help and psychological support immediately after the trauma, proactive identification, trauma-focused therapies and medications are beneficial. There is a need for further research in management and prevention of PTSD.

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## Part III

# STRESS AND SPECIFIC MENTAL DISORDERS



*Part III of the book focuses on the role of stress among specific psychiatric disorders, including alcohol and tobacco addiction, sleep, and sexual disorders. This part covers the role of stress among affective and non-affective psychotic disorders. The prevalence, role, and implications of stress among common mental disorders (depressive, anxiety, and somatization disorders) are discussed in these chapters. Both from a pharmacological and non-pharmacological management perspective of common mental disorders are also elaborated. Various stress related models are discussed about personality disorders. Modern-day psychiatric illnesses related to technological usage are also discussed. Sleep and sex are the two primary biological needs of human beings. The role of stress among these two biological needs is reflected in sleep, and sexual disorders are focused. Often stress is linked to higher usage of alcohol and tobacco use among the general population. The role of stress is covered in alcohol and tobacco addiction both in etiological*

*implications and management perspectives. An implication of suicide is one of the reasons for premature death among teenagers and young adults. In the last chapter, the role of stress in suicide and suicidal behaviour is also discussed from a clinical perspective.*

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## **STRESS & PSYCHOTIC DISORDERS**

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### **OUTLINE**

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| 1. INTRODUCTION                               | 2. PSYCHOSOCIAL STRESSORS AND AETIOLOGY OF PSYCHOTIC DISORDERS |
| 3. STRESS AND PSYCHOSIS:<br>THEORETICAL LINKS | 4. CONCLUSIONS   |

## **INTRODUCTION**

Earlier psychiatric nomenclature distinguished between neurosis and psychosis, where psychoses were considered to be a result of “somatic illnesses” and neuroses to be a result of “psychological biographic causes”(Bürgy, 2008). The meaning of the term “psychosis” has changed from the time it was first coined 170 years back (Beer, 1996), and is currently described based on clinical presentation rather than aetiology. According to the DSM-5, psychotic disorders are characterized by “abnormalities in one or more of the following domains: delusions, hallucinations, disorganized speech, grossly disorganized or abnormal motor behaviour (including catatonia) and negative symptoms”(Diagnostic and statistical manual of mental disorders, 2013). In this chapter, we restrict our discussion to non-affective psychoses to maintain focus and minimize overlap with other chapters.

As discussed earlier, psychosis has traditionally been considered to be of “somatic” or “endogenous” origin(Beer, 1996). Family and genetic studies have lent support to a strong genetic predisposition, exemplified by a high concordance rate of schizophrenia in monozygotic twins (45–60%), as compared to dizygotic

twins (10-15%)(Brown, 2011). However, it is equally clear that genetic factors cannot explain the predisposition for psychotic disorders completely. Population studies have suggested a heritability of 64% for schizophrenia(Lichtenstein et al., 2009). The remaining 36% of the predisposition could be attributed to non-heritable, including environmental causes. Epidemiological studies have identified a host of environmental factors associated with schizophrenia. These include perinatal infections, maternal nutritional deficiency, obstetric complications, paternal age, cannabis use, trauma, childhood infections, low socio-economic status, etc(Brown, 2011). Genetic and environmental factors are hypothesised to interact via a vulnerability stress model. In this chapter we discuss about a subset of environmental factors, namely, psychosocial stressors in the aetiology and prognosis of psychotic disorders.

The term “stress” has been used with different connotations and could include biological processes like oxidative stress, prenatal insults, stress response, etc. It has been used to indicate external or internal events that disturb the equilibrium as well as the body’s physiological response to such events. We have narrowed our discussion to psychosocial stressors which may have effect on psychotic disorders. We have not discussed other important environmental insults like neonatal hypoxia, obstetric complications, substance use, etc., which are known risk factors for psychotic disorders. We have discussed the role of psychosocial factors in the aetiology and course of psychotic disorders separately.

## **PSYCHOSOCIAL STRESSORS AND AETIOLOGY OF PSYCHOTIC DISORDERS**

### **Role of family in the Aetiology of psychotic disorders**

Earlier psychoanalytic theories attributed dysfunctional families or faulty parenting in the aetiology of schizophrenia. Deviant communication between parents and offspring were at the core of many of these theories. Some influential theories included the double – bind interaction(Bateson, 1956), marital schism and skew(Lidz, 1968), pseudo mutuality(Wynne et al., 1958), schizophrenogenic mother(Fromm-Reichmann, 1948), etc. These theories were postulated on the basis of clinical observations and research findings demonstrating communication deviances in families of patients with schizophrenia. However, further research found no differences in communication patterns between parents of schizophrenia patients and those of control offspring. Communication deviances can also

be observed in interaction between patients and others, suggesting that the communication deviance may be a consequence, rather than cause, of the illness (Liem, 1974). Adoption studies demonstrated that offspring of parents with schizophrenia have higher risks for developing schizophrenia have higher risks for developing psychosis even when raised apart (Ingraham & Kety, 2002). Children adopted into families where one of the adoptive parents had schizophrenia did not have a higher risk of developing schizophrenia than base rates (Wender et al., 1974). These studies suggest that genetic factors, rather than parenting, may be involved in the familial occurrence of schizophrenia. Twin studies have found that non-shared environment account for most of the variance in liability to schizophrenia attributable to environmental effects (Tsuang et al., 2001). Hence there is little evidence to support familial atmosphere in the aetiology of schizophrenia.

### **Role of other psychosocial stressors**

#### **Prenatal stress**

The neurodevelopmental hypothesis for schizophrenia posits that genetic factors and perinatal insults lead to aberrant neurodevelopment, which predispose the individual for developing schizophrenia in adolescence(Murray & Lewis, 1987). A recent meta-analysis found that parental psychopathology and maternal stress was associated with increased risk for schizophrenia(Davies et al., 2020). The evidence for particular stressors such as death of close relative or exposure to a catastrophic event during pregnancy has not been consistent(Brown, 2011; Davies et al., 2020). Maternal stress may be associated with altered glucocorticoid levels, altered immune activation, enhancement of the subcortical dopamine system and deficits in prepulse inhibition in the offspring which have strong association with schizophrenia(Markham & Koenig, 2011).

#### **Childhood adversity**

A meta-analysis found increased rates of childhood adversity in psychotic disorders (odds ratio 2.78) compared to controls(Varese et al., 2012). Prospective studies have found significant association between later development of psychosis and childhood adversities like bullying, maltreatment by adult and parental death(Pastore et al., 2020). Childhood trauma and other stressful events have also been found to be associated with schizotypy, with particularly strong associations found with positive schizotypy (Velikonja et al., 2015). A more consistent relationship has been found between positive symptoms and deficits in general cognitive ability (Heins et al., 2011; Dauvermann & Donohoe, 2018). Evidence from healthy as well

as psychotic populations point to a dose-response and bidirectional relationship between adversities and psychotic symptoms, indirectly supporting a causal effect of stress (Heins et al., 2011; Kelleher et al., 2013; Misiak et al., 2017). Childhood adversity is associated with most, if not all, psychiatric disorders (Kessler et al., 2010; Matheson et al., 2013). Hence the specific effect on its association with psychosis is questionable. Despite the non-specific nature, the pathophysiological link between psychosis and childhood trauma has been explained by various interesting theories which will be discussed in the later sections

### **Adulthood stressors**

There have been a few influential theories linking stressors in adulthood and psychotic disorders. The diathesis-stress model suggests that the genetic vulnerability of schizophrenia may require a later (possibly during adolescence) stressor to manifest psychosis(Jones & Fernyhough, 2007). The concept of reactive psychosis refers to an acute psychosis with good prognosis, emerging in response to a stressful life event (Ungvari et al., 2000). Beards et al (2013) reviewed the existing literature on the association between adult life stressors (>16 years) and onset of psychotic disorders(Beards et al., 2013). They found 16 relevant studies that included patients from both clinical and general populations (to study subclinical symptoms). The clinical studies included both first episode and non-first episode samples. Majority of the studies showed a positive association between adult onset stressors and onset of psychosis. Meta-analysis of 13 studies yielded an overall weighted odds-ratio (OR) of 3.19. There was significant methodological heterogeneity, including varied time period under consideration; it is difficult to exclude life events which might have been secondary to emerging psychosis. Due to the retrospective nature of most studies, a causal relationship cannot be inferred confidently (Lim et al., 2009). Studies evaluating the association of recent stressors and transition to psychosis in ultra-high-risk groups have been inconclusive (Mayo et al., 2017).

### **Urbanicity**

Urban residence has been found to be associated with increased rate of schizophrenia(Kelly et al., 2010). A meta-analysis of register-based studies on incidence rate of schizophrenia, found an OR of 2.37 (95% CI: 2.01-2.81) for the risk for schizophrenia at the most urban environment compared to the most rural background (Vassos et al., 2012). Interestingly, the prevalence of psychosis-like symptoms in a community sample has also been associated with level of

urbanicity (Van Os et al., 2001). Further, studies have also demonstrated a dose-response relationship for urbanicity and psychosis (March et al., 2008). Exposure to urbanization before, rather than around, the time of illness onset increase the risk for schizophrenia, suggesting that it increases the predisposition to schizophrenia (Marcelis et al., 1999).

Various mechanisms have been proposed to explain this association, including prenatal factors like nutritional deficiency, infections, obstetric complications; factors related to upbringing like socio-economic status, overcrowding, cannabis use; societal and community environment like socio-economic status, social disorganization, social fragmentation, and reduced social capital (Kelly et al., 2010). The association between urbanicity and incidence of schizophrenia has been found to be significant even after controlling for other confounding variables including age, marital status, socio-economic status, family history, obstetric factors, immigrant status, cannabis use, season of birth, exposure to cats etc. (Kelly et al., 2010).

The prevalence of schizophrenia is found to be higher in “inner-districts” which are purported to have higher social disorganization (Löffler & Häfner, 1999). Hence some authors have proposed a “social defeat hypothesis” for schizophrenia (vide infra)(Selten et al., 2013). However, one of the competing models is the “social drift” theory which supposes that people predisposed to or suffering from schizophrenia migrate selectively to urban areas due to various reasons like help seeking, job opportunities etc. The available evidence suggests that this association cannot be explained by social drift alone (Kelly et al., 2010; Heinz et al., 2013). Hence adverse social contexts such as population density, social fragmentation and deprivation might be contributing factors(Heinz et al., 2013). Interestingly, a Danish study found that living near a green space, especially during childhood, has a dose-dependent protective relationship against development of schizophrenia (Engemann et al., 2018).

It should, however, be noted that studies linking psychosis and urbanicity have not been entirely consistent, especially in non-western countries including India, Taiwan and Japan (Kelly et al., 2010; Jablensky et al., 1992; Varma et al., 1997; Chang, n.d.; Ohta et al., 1992). The inconsistency could be due to either methodological differences or cultural factors. As most of these studies are conducted based on population and case registers, the contribution of difference

in help-seeking between the urban and rural population cannot be ruled out. This is especially important considering that community based direct interview studies have not supported this association (McGrath et al., 2001; Perälä et al., 2008). Similar to childhood adversity, the effect of urbanicity does not appear to be specific for psychosis. A recent meta-analysis found a significantly higher prevalence rate for any psychiatric disorder in urban areas compared to rural areas, in particular mood and anxiety disorders (Peen et al., 2010).

### **Migrant population**

Ødegård (1932) was the first to demonstrate that Norwegian immigrants to USA had higher incidence of schizophrenia compared to native-born Americans and Norwegians residing in Norway (Ødegård, 1932). He explained the finding based on “the selective migration hypothesis” proposing that people predisposed to schizophrenia have higher chance of migration. Since then a number of studies of various ethnic populations have found a consistent increased risk of schizophrenia and other psychotic disorders in immigrants (Morgan et al., 2010). A relatively recent meta-analysis found that the incidence rate ratio for first generation and second-generation immigrants were 2.3 and 2.1 respectively (Bourque et al., 2011). This finding is slightly different from a widely-quoted earlier meta-analysis which showed higher risk in second generation immigrants compared to first generation immigrants (Selten & Cantor-Graae, 2005). Lower age at the time of migration was associated with a higher incidence of psychotic disorders among immigrants (Veling et al., 2011). Migrants from developing countries have greater risks compared to migrants from developed countries (Selten & Cantor-Graae, 2005).

Interestingly, risk due to migration seems to be specific to psychoses, as its effect on common mental disorders remains equivocal and may be dependent on other factors including social mobility (Kirmayer et al., 2011; Das-Munshi et al., 2012). This association can be explained in three ways: (a) selective migration hypothesis (Ødegård, 1932), (b) confounding biological variables and (c) the experience of migration functioning as a psychosocial stressor. A few studies have challenged the selective migration hypothesis (Selten et al., 2002; Van Der Ven et al., 2015). While research has failed to find excess of biological risk factors in migrants with psychosis in comparison to natives with psychosis (Morgan et al., 2010), in the absence of comparison with general population, their role in explaining the excess incidence of psychosis remains to be tested.

The more widely accepted hypothesis for the link between migration and psychosis is the psychosocial theory that suggests that migration acts as a psychosocial stressor in the form of increased social discrimination. In line with this hypothesis, the risk for psychosis is lower in populations with high immigrant density, possibly decreasing discrimination (Schofield et al., 2011; Termorshuizen et al., 2014). A cross-sectional study found a significant association between racial discrimination and risk of psychosis (Karlsen & Nazroo, 2002), although the direction of the association is conjectural. It has been proposed that repeated discriminatory and ‘threat’ experiences cause cognitive biases and affective states suggestive of paranoia. This is consistent with the evidence that persecutory delusions may be more common in migrant and minority ethnic groups (Morgan et al., 2010). Thus, it has been hypothesized that social discrimination may lead to marginalization and a state of ‘social defeat’ which predisposes to psychosis (Van Os et al., 2010).

### **Expressed emotions**

Psychosocial stressors have also been studied in the context of relapse of psychotic symptoms. Expressed emotions constitute an influential concept, which has been studied in relation to relapse in schizophrenia. Expressed emotions refer to the family environment, which includes the quality of interaction patterns and nature of family relationships among the family caregivers and patients with psychiatric disorders (Amaresha & Venkatasubramanian, 2012). The concept was introduced by Brown & colleagues who found that among discharged patients with schizophrenia, prolonged contact with family members was associated with increased risk of relapse and re-admission (Brown, 1959). It has been hypothesized that negative interactions between patients and family members act as psychosocial stressor which increases the risk of subsequent relapse. Expressed emotions have five dimensions including three negative dimensions namely criticism, hostility, emotional overinvolvement and two positive dimensions, namely warmth and positive regard. Studies have largely focused on the negative components. Family interactions which are high on negative dimensions are considered to have high expressed emotion. Systematic reviews show that EE is a consistent and robust predictor of relapse in schizophrenia (O'Driscoll et al., 2019). Expressed emotions are associated with more caregiver-related factors than patient-related factors. Hence, interventions to decrease expressed emotions usually include family psychoeducation, decreasing contact time with patients, problem solving and communication skills, strengthening the families' social support, and decreasing the caregiver's expectations on patients (Amaresha & Venkatasubramanian, 2012).

## STRESS AND PSYCHOSIS: THEORETICAL LINKS

Stressors during childhood and adolescence as described above affect the normal neurodevelopment contributing to the onset of psychosis. Various theories explain the link between such developmental stressor and psychosis. These theories are not mutually exclusive, but may act at different levels and there have been attempts to present a unified theory linking the following theories (Holtzman et al., 2013).

### Cognitive models

Despite being phenomenologically conceptualized as un-understandable, there have been recent attempts to explain psychotic experiences based on cognitive processes (Garety et al., 2001; Freeman et al., 2002). These theories postulate that in people with vulnerability to psychosis (due to biological, psychological and social factors), triggering events precipitate psychosis by causing anomalous experiences. The anomalous experiences may occur either directly due to the precipitating event or through intervening cognitive and emotional processes. These experiences are appraised in a faulty manner due to attributional biases/ maladaptive schemas leading to psychotic symptoms. In this model, psychosocial stressors are hypothesized to act at two levels. Early life adversities may lead to low self-esteem and negative schemata and beliefs about the self as vulnerable to threat, or about others as dangerous. Further, there may be later life events that trigger the onset of psychotic episodes. It has been hypothesized that trauma and adversity affect both information and emotional processing, leading to intrusions which are then misinterpreted and appraised as psychotic symptoms (Kuipers et al., 2006).

As discussed earlier, there is evidence for the role of early life adversity in psychosis, whereas the role of later life events has not been firmly established. Positive psychotic symptoms have been found to be associated with cognitive biases and negative cognitive schemas (Livet et al., 2020; LoPilato et al., 2020). Further, negative cognitive schemata have been found to at least partially mediate the link between childhood adversities and psychosis.

### Social cognition

Social cognitions like mentalizing ability, attribution, intention, self-representation, agency etc. are impaired in patients with schizophrenia(Van Os et al., 2010). Abilities like mentalization develop in preschool age and the development is

dependent on social interactions. When such interactions are affected by early life adversity, there is increased risk of development of psychotic symptoms. There is consistent evidence to link childhood adversity and social cognitive deficits in psychotic individuals(Kincaid et al., 2018; Rokita et al., 2020). Mentalization may mediate the association between emotional neglect and negative symptoms as well as disorganization in psychotic individuals (Mansueto et al., 2019). Further childhood trauma has been associated with social cognition related brain circuitry abnormalities in patients with schizophrenia(Cancel et al., 2017).

### **Social defeat hypothesis**

Selten & colleagues propose a common unifying factor between various well-established risk factors for schizophrenia including migration, urban upbringing, low IQ, childhood trauma, and illicit drug use in the form of social defeat (Selten & Cantor-Graae, 2005; Selten et al., 2013). The authors hypothesize “negative experience of being excluded from the majority group” as a common factor linking these stressors. The authors support their hypothesis based on the moderating effect of neighbourhood factors on the association between the above factors and risk of psychosis. Urban school children with social deprivation are protected against psychosis if majority of the children in the school are deprived (Zammit et al., 2010). Similar effect for minority status has been discussed above. Social defeat may lead to sensitization of the mesolimbic dopamine system as evidenced from animal studies, suggesting a biological plausibility for the hypothesis (Selten et al., 2013).

### **Social deafferentation hypothesis**

A parallel theory known as the social deafferentation hypothesis was proposed by Hoffman, who suggested that the risk factors for psychosis act via social isolation(Hoffman, 2007). Social isolation experiences are commonly seen in people before the onset of psychotic symptoms and this may lead to cortical reorganization. It is well-known that hallucinations and perceptual abnormalities occur during sensory deprivation and this has been hypothesized to be secondary to widespread cortical reorganization due to deafferentation (e.g. Phantom limb, Charles-Bonnett syndrome etc.). Similarly, social isolation during critical development period may lead to deafferentation to and subsequent reorganization of association cortices, which may lead to spurious experiences with social meaning in the form of positive psychotic symptoms.

### **Neurobiology of stress response**

An enhanced stress reactivity i.e. increased emotional reactivity to stressful life events including daily life hassles, has been observed in psychotic individuals compared to controls (Docherty et al., 2009; Myin-Germeys et al., 2001). Such increased reactivity has been seen in psychotic individuals, their first degree-relatives and also those in prodrome(Holtzman et al., 2013). Hence there is evidence for alteration in the stress response mechanisms in psychosis. Further, childhood adversity has been associated with increased stress reactivity in the form of increased emotional response to daily life hassles(Glaser et al., 2006; Lardinois et al., 2011).

The hypothalamus-pituitary-adrenal (HPA) axis hyperactivity has been observed in patients with psychosis and prodrome as evidenced by elevated baseline cortisol and ACTH levels compared with controls, non-suppression of cortisol in response dexamethasone suppression test and a blunted cortisol awakening response(Aiello et al., 2012; Borges et al., 2013; Holtzman et al., 2013). Blunted awakening response in the context of higher diurnal cortisol levels is unique to psychotic individuals(Borges et al., 2013). It has been suggested that the brain abnormalities associated with psychosis, may partially reflect the adverse effects of persistent glucocorticoid elevations on brain structure. Animal studies show that exposure to severe or persistent stress/trauma can heighten HPA reactivity and dopamine augmentation in response to subsequent stressors(Holtzman et al., 2013).

Thus, it has been hypothesized that psychosocial stressors increase the risk of psychosis through HPA axis abnormalities. Glucocorticoid secretion augments dopamine activity in certain brain regions, especially the mesolimbic system(Borges et al., 2013; Holtzman et al., 2013). Both migration and child adversity have been associated with elevated striatal dopaminergic function(Oswald et al., 2014; Egerton et al., 2017). A hyper-responsive dopamine response to stress has been observed in psychotic individuals and subjects with clinical high risk for schizophrenia (Mizrahi et al., 2012). This enhanced dopamine response may increase the salience of events leading to positive symptoms of psychosis. HPA axis may also act via other neurotransmitter systems like GABA or glutamate(Holtzman et al., 2013).

### **Neuroinflammation**

The “neuroimmune hypothesis of schizophrenia” has been proposed based on genetic studies and studies demonstrating increased pro-inflammatory markers in

schizophrenic individuals(Buckley, 2019; Pedraz-Petrozzi et al., 2020). Childhood adversity is associated with elevated levels of various inflammatory markers, especially cytokines in adulthood. Thus, neuroimmune mechanisms, which may be modulated through HPA axis, may mediate the relationship between stress and schizophrenia. Microglia have been implicated in the stress related immune response in schizophrenia(Howes & McCutcheon, 2017).

### **Gene-environment interactions**

As discussed earlier, many with genetic predisposition do not develop psychosis, as evidenced in twin and family studies. Similarly, the environmental insults hypothesized in schizophrenia are far too prevalent, and most individuals exposed to them do not develop schizophrenia. Thus, neither of these factors appear to be sufficient in themselves to cause schizophrenia, and a gene-environment interaction is necessary in explaining the cause of schizophrenia.

In two population studies, it has been demonstrated that there is significant interaction between urbanicity and family history in the risk for schizophrenia(Van Os et al., 2003, 2004). However, studies on developmental trauma and family liability could not demonstrate a gene-environment interaction(Alemany et al., 2013; Wigman et al., 2012; Fisher et al., 2014). Interactions with childhood adversities have been demonstrated in candidate gene studies focusing on dopaminergic genes (especially the COMT gene) and genes regulating HPA axis(Collip et al., 2013; Ajnakina et al., 2014; Vinkers et al., 2013; Ramsay et al., 2013). Recent studies employing polygenic risk score calculated based on large genome wide association studies ('Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci.', 2014) have found an additive effect for gene-environment interaction (Guloksuz et al., 2019; Mas et al., 2020).

### **Epigenetic mechanism**

Epigenetics refers to the process of "changes in gene function, heritable through mitosis and meiosis, that do not involve changes in DNA sequence" (Maric & Svrakic, 2020). Epigenetic modifications can occur in response to environmental influences and are reported to have acute effects, can target specific tissues and may also be transmittable. The mechanisms of epigenetic modifications include DNA methylation, histone modification and non-coding RNAs (Diwadkar et al., 2014). Epigenetic modulations of genes regulating neurodevelopment, immune function

and neurotransmission have been associated with schizophrenia (Smigelski et al., 2020). It has been postulated that epigenetic modulations secondary to early life stressors may manifest as “molecular scars”, that may increase the predisposition to schizophrenia (Richetto & Meyer, 2020). For example, recent evidence suggest that histone deacetylase (HDAC), a modulator of epigenetic mechanisms, may mediate the link between childhood adversity and schizophrenia (Bahari-Javan, 2017).

## **CONCLUSIONS**

Early life stress may increase the risk of subsequent development of psychosis. However, the specificity of this effect for psychosis is questionable as early adversity is a risk factor for most psychiatric disorders. The influence of stressors later in life has been less conclusive. Methodological limitations and diversity of the studies on later life stressors make it hard to draw firm conclusions. Other risk factors like urban upbringing and migration are consistently associated with development of psychosis. Studies that have controlled for potential confounders of this association have also found a significant association suggesting that these may act as a social stressor. These factors are far too prevalent in the general population to suggest a clear one-to-one relationship. Most patients exposed to such factors do not develop psychotic illness. Hence these may at best be considered risk factors. Most established risk factors for psychotic disorders seem to act at an early age –e.g. genetic factors, perinatal complications, early life stressors etc. Further, the effect of urbanicity and migration is more prominent when they occur at an early age. This is consistent with neurodevelopmental model of schizophrenia, where the genetic and environmental risk factors are purported to disturb the normal developmental process leading to onset of psychosis at a later age.

Most preventive programs for psychotic disorders focus on indicated prevention during the prodromal phase or early psychosis(Stafford et al., 2013). Understanding the risk factors associated with development of psychosis could help in the development of primordial prevention efforts. A lot remains to be known about genetics of psychoses. Given that genetic counselling has additional ethical challenges, at present, primordial prevention targeting psychosocial stressors holds promise.

Improving obstetric care to reduce maternal infections, obstetric complications, nutritional deficiency etc., are relatively straightforward and can be achieved as part

of larger programmes to improve maternal and child care services. Psychosocial stressors are ubiquitous and inherent part of the human existence and cannot be entirely prevented. However, efforts to mitigate the effects of such stressors can certainly be made. Systemic, community-level interventions towards reducing and managing child abuse and maltreatment would go a long way in the prevention of mental health problems in general, if not for psychosis in particular. These would include community awareness and stringent legal measures to reduce the occurrence of child abuse and provision of services to mitigate the effects of child abuse. The challenges of risk factors like urbanicity and migration extend beyond the considerations of psychiatric conditions. Social interventions addressing factors like overcrowding, social defeat and discrimination, with the larger welfare of individuals in mind may, in addition, mitigate the risk of development of psychosis to some extent. Community and systemic interventions towards better integration of immigrants and decrease overcrowding in urban communities have been suggested to mitigate the risk of psychosis (Brenner et al., 2010). However, the current understanding is still inadequate for advocating such policy level changes solely for prevention of psychoses. Finally, measures to improve adolescent mental health, particularly in terms of managing stress, improving coping skills and preventing substance abuse have potential to prevent psychoses as well. In contrast to such primary prevention measures which are generic in nature and potentially expensive, mental health professionals have scope for indicated and secondary prevention. There is need for research and dissemination of interventions focusing on psychosocial stressors, that decrease the risk of transition from at-risk states and prevent relapse of illness.

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## **STRESS AND SOMATIC SYMPTOM DISORDERS**

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**OUTLINE**

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|--|---|
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### **INTRODUCTION**

Stress has been defined as an environmental demand that individuals appraise as heavily taxing or exceeding their coping abilities(Lazarus & Folkman, 1984). Stress comprises of two components: the presence of a stressor (i.e., demand from an individual's environment) and the subjective experience of stress due to the presence of this stressor (i.e., the appraisal that the stressor taxes the coping abilities). The nature of stressors may be predominantly physiological or predominantly psychosocial.

Stress is a component of everyday life but difference exists amongst the individuals in their response to the stressful life events which involves activation of various biological systems which, though necessary for survival, on a long term may lead to medical problems.

The impact of physiological stress reactions on the developing brain may be of particular note, helping to explain how adverse rearing experiences heighten the risk of behavioural and emotional problems in children and adolescents. Any medical illness is characterized by subjective complaints of the symptoms by the patients and the objective signs, which the physician elicits during examination. Presence of both implies that a person is suffering from illness. However, in some conditions, only subjective complaints are present in the absence of objective findings.

The term somatization has been in use for many decades. Lipowski (1968) has defined *somatization* as the “tendency to experience or express psychological distress as the symptoms of physical illness”. Somatic symptoms are the most common cause of visit to a general practitioner, of which 33% of the somatic symptoms are unexplainable medically(Kroenke, 2003). These medically unexplained symptoms are a cause of significant concern as they lead to significant personal suffering and poor quality of life(Kirmayer *et al.*, 2004).

Little is known about the pathophysiology of the experience of above symptoms. Though cognitive and perceptual processes play an important role, biological factors are also equally important. Medically unexplained somatic symptoms are not fully explained by any single mechanism and a multifactorial approach is needed. Recent research and theory in this area show complex interactions between cognitive-perceptual, psychobiological components in the development and perpetuation of medically unexplained symptoms. Somatoform disorders are conditions characterized by recurrent physical symptoms for which there is no evidence of physical illness. ICD 10(World Health Organization, 1992) and DSM IV(American Psychiatric association, 1994) have specific diagnostic criteria based on the number of symptoms and duration of symptoms. DSM V(American Psychiatric association, 2013) has revised the diagnostic criteria of somatoform disorders to Somatic symptoms disorders. The number of symptoms is no longer a criterion for the diagnosis of somatic symptoms disorders. Also, the number of disorders and subcategories have been reduced to avoid overlap. Diagnosis of somatization disorder, pain disorder, hypochondriasis and undifferentiated somatoform disorder have been removed. Patients previously diagnosed with somatization disorder will receive the diagnosis of somatic symptom disorder only if they have maladaptive feelings, thoughts and behaviours that define the disorder along with somatic symptoms. And because of arbitrary distinction between

somatization disorder and undifferentiated somatoform disorder, they now have been merged in DSM 5 under somatic symptom disorder.

## **EPIDEMIOLOGY OF SOMATIC SYMPTOMS**

Typically, a third to half of the presented symptoms remains unexplained in primary care and population based studies, and of this group of Functional Somatic Syndrome (FSS), 25% are chronic or recurrent(Kroenke & Rosmalen, 2006).

While FSS are common, somatization disorder is a very rare diagnosis with an estimated prevalence of 0.03 – 0.84% in the general population(Creed & Barsky, 2004). Prevalence of undifferentiated somatoform disorder and somatoform disorder NOS have not been surveyed in the general population, but almost 30% of primary care consulters meet the diagnostic criteria(Fink et al., 1999).

In a study in elderly patients examining war related and civilian trauma related experiences during adolescence and childhood, 11.5% of the patients experienced posttraumatic war related symptoms which met the criteria for somatoform syndrome and around 9 % individuals met criteria for major depression(Glaesmer et al., 2012).Also in a study of evaluating psychiatric morbidity in tortured Bhutanese refugees in Nepal, more than half of the tortured group had lifetime history of persistent somatoform pain disorder(Van Ommeren et al., 2001).

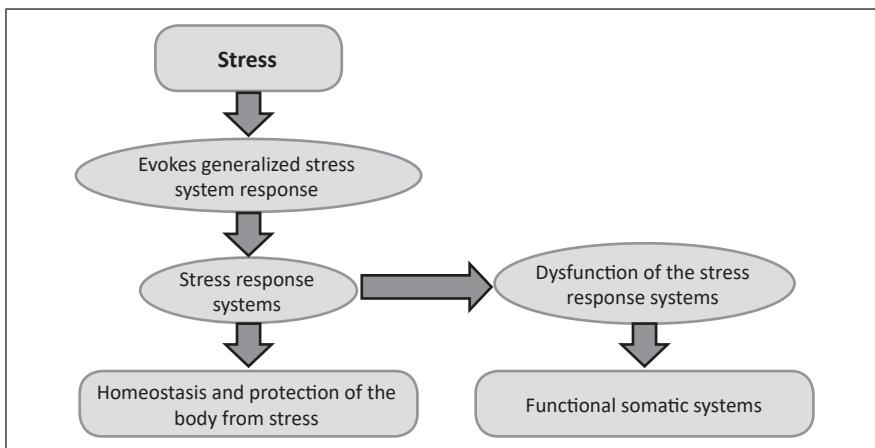
## **RELATIONSHIP OF STRESS AND SOMATIZATION**

Stress has been considered as a causative or a maintaining factor in somatoform disorders. Hence it is important to understand the relationship between the stress and somatization. The possible relationship stress and somatization stems from the fact that these stress systems increase the somatic symptom perception and experience(Sharpe & Bass, 1992). It is often considered as a possible mediator between the psychosocial stress and somatization and long-term psychosocial stress leads to chronic under or overactivity of the stress responsive systems.

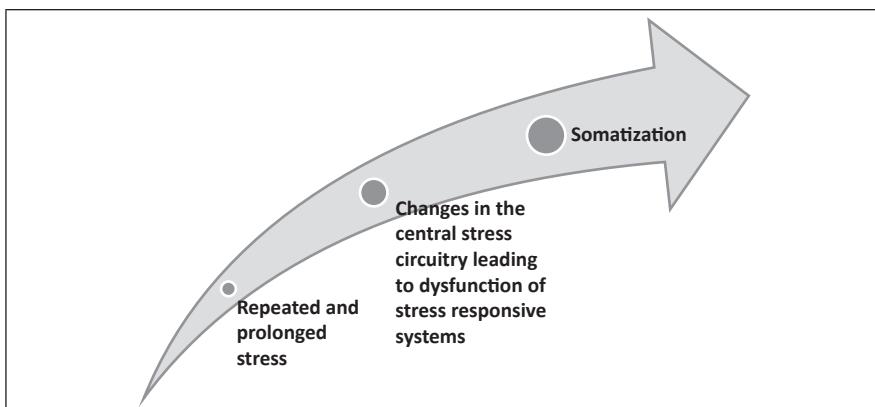
Chronic stress has an important part to play in the development and maintenance of functional somatic symptoms. Virtually all models on the aetiology of somatization include forms of psychosocial stress. Stress responsive system as one of the most important mediators between psychosocial stress and somatization has received considerable research interest in the last two decades but still the evidence

appears bleak for it to be one of the potential biological mediators between the two. It has been assumed that dysfunction of stress responsive systems, consisting of alterations in activity of the autonomic nervous system (ANS), hypothalamic-pituitary-adrenal (HPA) axis, and immune system, contributes to somatization. The reasons that have been considered for dysfunction of stress responsive systems include: increased load of stressors in an individual, chronic recruitment of stress responsive systems, or the diminished capacity of the stress responsive systems to adjust (Chrousos & Gold, 1992).

**Figure 1: General overview of relationship between stress, stress response systems and somatic symptoms.**



**Figure 2: General overview of relationship between stress, stress response systems and somatic symptoms (Continued).**



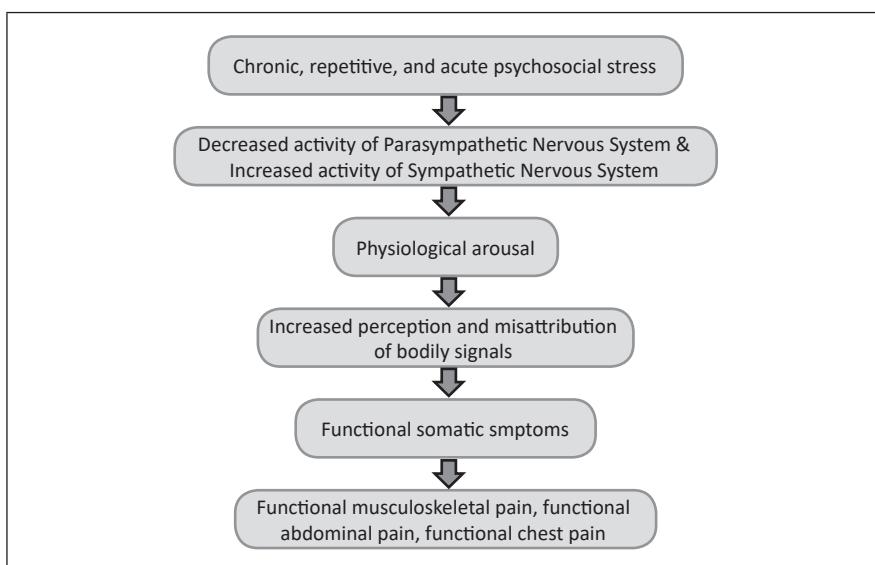
## INDIVIDUAL STRESS RESPONSIVE SYSTEMS

### 1. The Autonomic nervous system

One of the mechanisms of the genesis of the FSS could result from heightened physiological activity which would result in increased perception and misattribution of bodily signals. Also as per Pennebaker's model, the perception of physical symptoms is determined by the intensity of the interoceptive signal itself divided by the intensity of external stimulation ('distraction')(Pennebaker, 1982). Hence increased physiological activity would be a contributory factor for the development of physical signals.

Activity of the autonomic nervous system is influenced by chronic, repetitive and acute psychosocial stress(Dishman *et al.*, 2000)(Schommer *et al.*, 2003).

**Figure 3: How this chronic stress leads to development of FSS.**



(Sharpe & Bass, 1992)(Rief & Barsky, 2005)

Heart rate variability which is the most common measure for ANS function, represents inter beat interval fluctuations in heart rate (HR). Studies which have measured resting parasympathetic nervous system activity in functional somatic disorders (i.e. in CFS, IBS and FM) have shown decreased cardiac vagal activity (Lineke M Tak & Rosmalen, 2007).

However, there are no studies examining the relationship between ANS function in somatization disorder, pain disorder, undifferentiated somatoform disorder, or somatoform disorder NOS.

In a study examining the heart rate activity after a mentally distressing task, which normally decreases after the tasks completion, was found to be constant in patients with somatoform disorder(Rief & Auer, 2001)

## 2. HPA axis

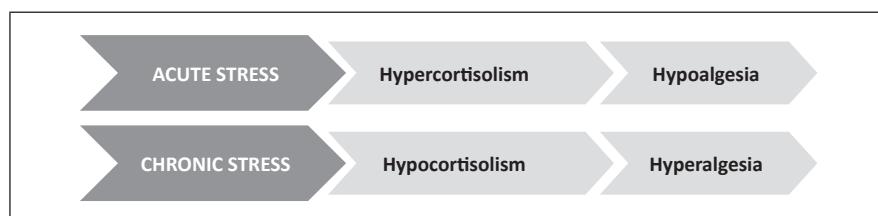
Various components of the HPA pathway and alterations in the concentration of CRH, ACTH and cortisol may be involved in somatoform disorders.

There are no studies of HPA axis activity in somatization disorder, pain disorder, undifferentiated somatoform disorder, or somatoform disorder NOS. Two studies that used a less restrictive definition of somatization disorder found either no alterations (Rief & Auer, 2000)or higher levels of cortisol in the patients(Rief et al., 1998).

A longitudinal population-based cohort study investigated the association of HPA axis function with cross-sectional presence and prospective development of FSS in the general population found neither cross-sectional association between 24-hour Urinary Free Cortisol (UFC) excretion and the number of FSS nor associated with any of the bodily system FSS clusters and also did not predict new-onset FSS in the 2-year follow-up period. The authors concluded that the study does not provide evidence for an association between altered HPA axis function, as indexed by 24 hour Urinary Free Cortisol(UFC), and FSS in the general population(Lineke M Tak et al., 2009).

As summarized in the review by Winfried Rief, 2005 (Rief & Barsky, 2005)

**Figure 4: Stress and pain perception**



Role of HPA-activity in the pathophysiology of somatoform conditions is still unclear with no definitive and consistent findings.

### 3. Immunological perspective

A convergence of evidence suggests that prolonged pro-inflammatory signalling is a critical component of the pathophysiology underscoring stress related psychiatric disorders(Maes *et al.*, 1999)(Straub, 2006).

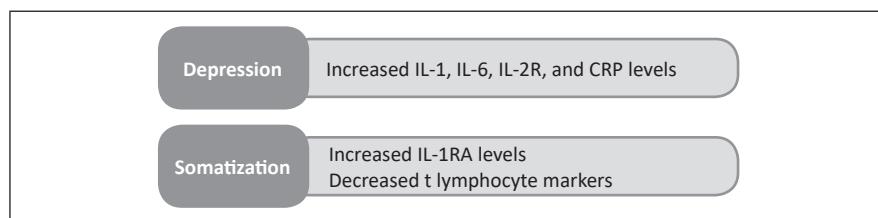
As certain cytokines can stimulate inflammatory pain as per studies by Schaefer & Stein, 1999, it could be hypothesized that the pain symptoms in somatoform disorders could be mediated by cytokines(Anderson *et al.*, 2014).

Sickness behaviour induced by cytokines has features of somatic symptoms, for e.g. hyperalgesia, impaired sleep, and fatigue as per animal studies, that overlap with patients with somatoform disorders(Dantzer, 2001)(Wieseler-Frank *et al.*, 2005).

Depression and somatization have been studied in the context of IL-1RA, T-lymphocytic markers such as sCD8, and endogenous anti-inflammatory substances including CC16 (uteroglobin/Clara cell protein), there are significant variations of these biomarkers in these disorders. While depression is characterized by increased serum IL-6 and sCD8, both of these factors are significantly decreased in somatization. Depression is characterized by reduced serum CC16, whereas there are no significant alterations in serum CC16 in patients with somatization.

A recent study shows that patients with somatization have increased Tumour Necrosis Factor (TNF  $\alpha$ ) and neopterin levels, indicating activation of immuno-inflammatory pathways. All in all, depression is accompanied by monocytic and CMI activation and by lowered endogenous anti-inflammatory defences, while somatization is accompanied by monocytic activation(Euteneuer *et al.*, 2012).

**Figure 5: Relationship between depression, somatization and immune-inflammatory pathways.**



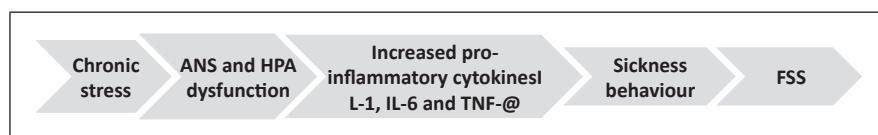
Studies in somatization patients, in which a less restrictive form of definition was used, found lower levels of pro-inflammatory cytokines in contrast to the higher levels hypothesized in the pathophysiology of the disorder (Euteneuer *et al.*, 2012). The hypothesis suggested was that the finding was due to alterations in the central level of cytokines which are typically not measurable in the peripheral blood. Also, high-sensitivity CRP (hs-CRP) was not found to be a biomarker for the total number of FSS in the general population.

Kiecolt-Glaser *et al.* showed that the body's immune system can also be triggered by non-pathogenic signals like psychosocial stressors(Kiecolt-Glaser *et al.*, 2002). As per a metanalysis, chronic stressors are associated with negative effects on all the functional measures of the immune system (Segerstrom& Miller 2004). In a population-based study of older adults, higher levels of chronic stress were associated with higher concentrations of IL-6 and CRP(Ranjit *et al.*, 2007).

### **Pathways Linking Immune Dysregulation and Somatization**

The immune system may be related somatic symptoms via sickness behaviour, which includes a combination of non-specific symptoms including fatigue, weakness, malaise, hyperalgesia, and increased focus on own body, induced by pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-  $\alpha$ . Also, immune activation may be a marker for activity of the ANS and HPA axis, as both systems closely interact with the immune system(Dantzer, 2001)(Wieseler-Frank *et al.*, 2005)(McEwen *et al.*, 1997)(Araújo *et al.*, 2006).

**Figure 6: Pathways linking immune dysregulation and somatization.**



Patients with somatoform disorders are likely to have alexithymia. As patients with alexithymia exhibit increased bodily symptoms due to inability to express emotional distress, it could be related to immune disturbances namely, altered CMI or cytokine levels(Dewaraja *et al.*, 1997)(Corcos *et al.*, 2004). Serum levels of IL-6 and IL-10 were found to be significantly increased in patients with SFD in comparison to healthy controls. It was also reported that there was a negative correlation between the level of alexithymia (total TAS-26 score) and the serum levels of sIL-2 R $\alpha$  (Pedrosa Gil *et al.*, 2007). Taken together these results suggest

that SFD, with clinically significant alexithymia, are associated with a reduction in TH1 mediated immune function and an increase in the activation of the TH2 immune function, indicated by the augmented serum levels of the interleukins. They concluded that alexithymia is associated with chronic activation of the immune system and may be critically involved in the pathophysiology of bodily symptoms in SFD.

### **Oxidative and nitrosative stress (O&NS) and Autoimmunity**

Immune-inflammatory pathways are involved in the regulation of redox oxidant status and the subsequent generation of oxidative and nitrosative stress which along with the reduced antioxidant levels is evident in depression and functional somatic disorders (Maes, 2011)(Maes *et al.*, 2011)(Jacka *et al.*, 2012).

Increased Reactive Oxygen Species (ROS) damages the cell membranes of the organelles leading to development of auto-immunity and subsequent serotonin autoantibodies and serotonin depletion. Serotonin transmission abnormalities can also occur due activation of indoleamine 2,3-dioxygenase (IDO) by immuno-inflammatory mediators or tryptophan 2,3-dioxygenase (TDO) induction due to glucorticosteroids in depression. Increased Interferon (IFN) cytokine and proinflammatory cytokine activate IDO and, subsequently, lower plasma tryptophan and thereby serotonin.

Also the activation of the Tryptophan catabolites (TRYCAT) by proinflammatory cytokines alters neuronal activity contributing to depression and somatization, not simply via decreased serotonin but by the induction of significant neuronal modulators such as quinolinic acid (QUIN), picolinic acid, and xanthurenic acid which have neuroregulatory activity (Anderson *et al.*, 2014). Alterations in the TRYCAT pathway also plays a role in the onset of somatization.

In a study comparing depression, somatization, depression and somatization, and controls, reported a finding that plasma Tryptophan (TRP) was lowest in individuals with somatization. Importantly, the Kynurenine (KY), Kynurenine (KY)/Kynurene Acid (KA), and KY/TRP ratios were significantly increased in somatization as compared with depression and control subjects, with plasma KA levels being significantly lower in patients with somatization. Plasma tryptophan and KA levels negatively correlate with the severity of somatization. (Maes *et al.*, 2011)

### **How Stress Leads to Increased Inflammation**

Psychological stress in humans may induce the production of pro-inflammatory cytokines and O&NS, such as increased lipid peroxidation and oxidative/nitrosative DNA damage.(Maes *et al.*, 1998)(Aleksandrovskii *et al.*, 1987), (Sivonova *et al.*, 2004)(Irie *et al.*, 2001). Psychological stress induces the immune-inflammatory O&NS pathways and reduces antioxidant defences. Hence, treatments that inhibit IO&NS pathways have anti stress effects.

In view of the evidence linking inflammation and HPA axis activation it is possible that stress, which activates HPA axis might influence and hence have a role in pathophysiology of the immune-to-brain communication. Cross-sensitization between stressors and cytokines exists. Exposure to stress, for instance, sensitizes the peripheral as well as central cytokine responses. Additionally, sensitization can also occur when the same cytokine is administered twice at an interval of several days or weeks, and it affects both cytokine-sensitive neurotransmitter metabolism and pituitary-adrenal responsiveness to cytokines.(Johnson *et al.*, 2002)(Tilders *et al.*, 1999)(Anisman *et al.*, 2003)

Sympathetic and Parasympathetic nervous system mediate the effect of stress on immune system in opposite directions with the former increasing the inflammatory response and the latter reducing it.(Lineke Maria Tak, 2010)

### **Signal Filter Model for Somatoform Disorders**

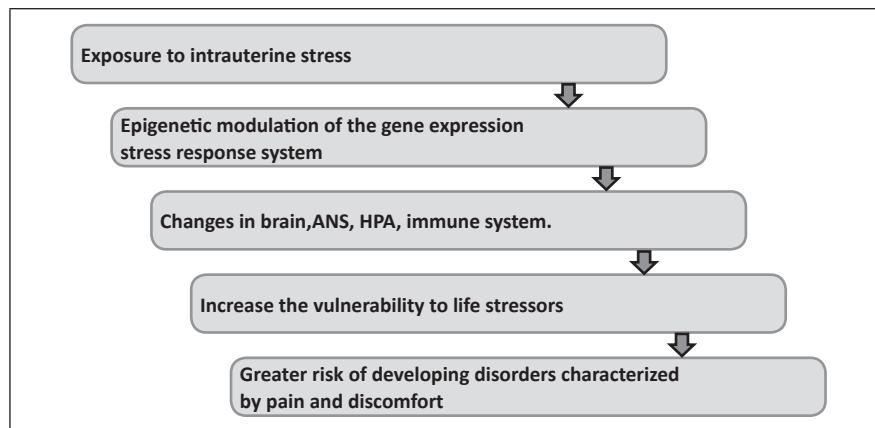
There exists a neural filtering process which does not permit all the generated signals from reaching brain and subsequent perception. Hence as per this model, the aetiology for the generation of unexplained physical sensations is misperceptions due to amplified sensory signals or decreased filtering capacity. Amplified physical sensations can be due to increased arousal or chronic HPA axis activation. The above theory is in concordance with the **cognitive activation theory of stress** which postulates that stress leads to increase in physiological signals. In the absence of substantial distraction, a rule in distressing situations, this leads to significant symptom perception as is seen in chronic high arousal states.

### **Early life Stressor**

During pregnancy, when the mother is exposed to a stressor which is severe and harsh, the stress hormones may cross the placenta and can cause alterations in the foetal development and lead to changes in the foetal stress response function and

brain. These may also predict the vulnerability to stressors later in the life. Adults vary in their responsiveness to a stressor which is probably due to epigenetic modulation of their genes regulating stress response system which in a long run leads to alterations in the HPA axis functioning. It has also been observed that this increases the vulnerability to develop disorders related to stress. There is evidence of adverse early life experiences in many studies of patients with medically unexplained symptoms and somatoform disorders.

**Figure 7: The mechanism of influence of early environmental adversities in the development of MUS is depicted by the figure below.(Buffington, 2009)**



## STRESS AND SOMATIC AMPLIFICATION

There exists significant cross-sensitization between stressors and cytokines which have an important role in pathophysiology of somatic amplification. Prior exposure to either of these, sensitizes the response to the other. Also, the perception of pain is strongly amplified under the effect of proinflammatory mediators. The major implication of this is that many somatization symptoms are a result of the expression of a previously sensitized brain cytokine system that is reactivated by infectious or non-infectious trauma.

## MANAGEMENT OF SOMATOFORM DISORDERS

Under recognition of the somatic symptom disorder and its under-treatment is common considering the poor conceptual clarity and lack of definite treatment options.

Treatment should be initially symptomatic (pharmacological) in order to relieve the distress of the patient before more definitive treatment targeting the aetiology can be instituted (e.g. CBT). The treatment of somatoform disorders is multimodal as none of the method on their own provide a satisfactory outcome.

Pharmacotherapy is the most common method of intervention in routine clinical practice. Evidence for pharmacological management is tilted in favour of antidepressants and treatment is governed by the symptom profile and the tolerability. SSRI's and SNRI's act both peripherally and centrally in reducing the perception of pain and other somatic symptoms in patients and the analgesic effect may also be due to interaction with opioid systems. Medications with positive trials are nefazodone, fluvoxamine, escitalopram, fluoxetine, opipramol, venlafaxine and mirtazapine(Somashekhar *et al.*, 2013). A meta-analysis of 11 randomized control trials concluded that tricyclic antidepressants decreased pain intensity significantly compared to placebo (Fishbain *et al.*, 1998). Other drugs with some efficacy in treatment of somatoform disorders are levosulpiride (Altamura *et al.*, 2003) in reducing a number of symptoms in a double blind placebo controlled cross-over study of patients with somatoform disorder and Topiramate (García-Campayo *et al.*, 2002) in an open label trial of patients with multi somatoform disorder in reducing pain symptoms.

As per psychological conceptualization of somatic symptoms, it is either considered a consequence of psychological disorders like depression or anxiety, as a part of help seeking behaviour, or as a way of responding to stress.

It can also be conceptualized as per “somatosensory amplification model” which includes hypervigilance to bodily sensations, selecting out and amplification of weak sensations, and intensifying of these sensations by cognition and affect(Barsky, 1998).

The biopsychosocial model focuses on consequences rather than the causes of symptoms, thus treating physical symptoms rather than the cause is a priority by considering various factors involved in the perception and maintenance of symptoms (Sharpe *et al.*, 1992).

The psychological interventions that have been found to be useful can be classified broadly into two categories(Sharma & Manjula, 2013):

- 1) Those developed for practice by general practitioners.
- 2) Those developed to be used by trained therapists.

Those which were developed for practice by general practitioners include:

- a) Psychiatric consultation intervention (consultation letter)

Those developed to be used by trained therapists include:

- a) Symptom clinic intervention
- b) Reattribution therapy
- c) Cognitive –behavioural therapy
- d) Problem-solving approach.

## **CONCLUSIONS**

Stress has an important role in somatic symptoms disorders. Early life stressors could result in susceptibility to develop somatic symptoms disorders. The relationship between stress and somatization is complex. Stress can lead to changes in the HPA axis, ANS and immunological changes which could lead to somatic symptoms disorders.

Repeated activation of the stress systems, especially during the vulnerable period of development leads to increase in the vulnerability for physical and mental disorders, including somatoform disorders by leaving permanent imprints in the neural substrate of emotional and cognitive processes.

However, despite significant advances in our understanding of the relationship between stress and somatoform disorders, there is still a great deal that is not understood. Somatoform symptoms have biological components that have an important role in creating a vicious circle together with cognitive, behavioural, and emotional features. But the evidence of pharmacological and non-pharmacological interventions to attenuate the somatic symptoms is weak and much research is desired in this regard.

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## **STRESS AND DEPRESSIVE DISORDER**

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### **OUTLINE**

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## **INTRODUCTION**

Over 300 million people across the globe, equivalent to 4.4% of the world population, suffer from clinical depression (WHO, 2017). The DSM-5 (American Psychiatric Association, 2013) diagnosis of clinical depression – major depressive disorder (MDD) is multifactorial in aetiology and heterogeneous in presentation. Of all the various mental disorders, MDD causes the heaviest burden, accounting for 2.5% of all global disability-adjusted life years (DALYs – the total number of years lost to illness, disability, or premature death in a given population) (Murray et al., 2010).

The aetiological factors causing depression are yet to be fully understood. Schildkraut (1965) proposed the monoamine imbalance hypothesis conceptualising depression as resulting from disturbed monoamine neurotransmission. This remains the most widely accepted hypothesis. However, multiple other aetiological mechanisms are likely at play and the hypothesis has proven unsatisfactory in explaining these other phenomena found in depressed patients. These include the

changes in other neurotransmitter systems, the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, the macroscopic and microscopic structural brain changes or even the relatively recent findings of altered gut microbiota (Mayer et al., 2014) and inflammatory changes (Rosenblat et al., 2014). During the last decade, neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) (Numakawa et al., 2014) and epigenetic mechanisms, for example, histone modifications and DNA methylation (Sun et al., 2013), have also been suggested as playing an important role in the aetiology of depression.

Genome-wide association studies (GWAS) in humans have been unable to establish genetic loci that contribute to MDD consistently (Bosker et al., 2011). Hence, contemporary thinking regarding the aetiology of depression suggests that genetic predisposition and environmental factors, such as stress, converge to produce a set of dysfunctional affective, behavioural, cognitive and physiological states, manifesting as the heterogeneous symptom-complex of MDD. Indeed, various investigators have estimated that one-third of the risk for developing depression is inherited, and two-thirds is environmental (Sullivan et al., 2000; Nemeroff, 2003). The link between exposure to stressful life experiences and the subsequent development of depression has received considerable attention since the seminal book – *The Social Origins of Depression* – was published on the topic in 1978 by George Brown & Tirril Harris. Further evidence of a strong association between exposure to stress and depression has since been amassed (Kessler, 1997; Paykel, 2001; Tennant, 2002). Clarity regarding the mechanisms by which stress exerts depressogenic effects is of much import as this will help not just in the preventative aspects of managing the illness, but also in the development of novel antidepressants in the future.

Author will briefly recapitulate the workings of each of the individual constituents of the stress system. The neurobiology of depressive illness is described in each individual section that details the normal stress response mounted by the individual parts of the stress system. Apart from this neurobiological perspective, we will consider pertinent psychological perspectives regarding the link between stress and depression, followed by a consideration of the implications for prevention and treatment.

## THE NEUROBIOLOGICAL MECHANISMS OF THE STRESS RESPONSE AND ITS DISORDER IN CLINICAL DEPRESSION

These include:

- AFFECTIVE, BEHAVIOURAL AND COGNITIVE RESPONSES
- PSYCHOENDONEUROIMMUNOLOGICAL RESPONSES
- NEURO-GENERATIVE RESPONSES

### Affective, Behavioural and Cognitive Responses

#### a) The Normal Response

The normal stress response has evolved to restore homeostasis in an individual who is faced with stressors that threaten to disturb this state of homeostasis. A mild state of anxiety is established, as anxiety is necessary for survival during stress. During non-stressed periods, the subgenual prefrontal cortex keeps the amygdala in check. However, during stress, its control over the amygdala diminishes, allowing the disinhibition of the amygdala, resulting in anxiety (Simpson et al., 2001). Meanwhile, the dorsolateral prefrontal cortex, which subserves working memory and controls cognition associated with fear, also gets downregulated during stress (Arnsten, 2009). The activated amygdala inhibits the subgenual and dorsolateral prefrontal cortices as well as activates the HPA axis, locus coeruleus–noradrenaline system and the sympathetic nervous system (Gold et al, 2015).

The anxiety adaptively biases attention to the threatening stressor. The ability to shift set away from the stressor is reduced partly due to the downregulation of the ventrolateral prefrontal cortex (Gold, 2015).

The amygdala and hippocampus store emotional memories which are retrieved during stressful situations, this being facilitated by cortisol and noradrenaline (NA) secreted during stress, facilitating adaptation to the ongoing stressor (McGaugh, 2004).

In acute stress, the activity of the nucleus accumbens increases due to cortisol secretion – helping maintain a disposition to deal with the stress at hand. However, in chronic, severe stress, hypercortisolism suppresses the nucleus accumbens (Gold et al, 2015). Hedonic tone can interfere with the ability to focus on stress, hence there is a need to reduce the ability to feel pleasure during a stressful situation. The ventral tegmental area in the brainstem sends dopaminergic projections to

the nucleus accumbens – the seat of the reward centre (Berridge & Kringelbach, 2013). The subgenual prefrontal cortex regulates the nucleus accumbens, hence, when stress impacts this area of the prefrontal cortex by reducing its activity, this hampers the functioning of the nucleus accumbens too (Drevets et al., 2008; Price & Drevets, 2012).

**b) The dysregulated stress response leading to depression**

Clinical experience has shown that anxiety is frequently comorbid with depression. Research confirms that anxiety disorders may coexist in up to 60% of clinical depression cases (Kaufman & Charney, 2000). In depression, significant abnormalities are seen in the subgenual anterior cingulate cortex – its volume has been shown to decrease by 40% (Drevets et al., 2008), while its metabolic activity increases (Drevets et al., 1997), denoting its stressed state. These changes reduce its control over the amygdala, which, in turn, shows increases in volume and metabolic activity. This results in increased anxiety (Drevets et al., 2008; Price & Drevets, 2012). The reduced volume of the subgenual anterior cingulate cortex has been attributed to hypercortisolemia, raised noradrenergic drive, reduced serotonin neurotransmission, glutamate toxicity, and a stimulated amygdala (Puig & Gullede, 2011). Indeed, an activated amygdala and a suppressed subgenual prefrontal cortex can lead to a vicious cycle perpetuating the dysregulated affective response to stress. Of note, in refractory depression cases, deep brain stimulation of the subgenual anterior cingulate cortex has been used to good effect (Mayberg et al., 2005).

Inhibited functioning of the dorsolateral prefrontal cortex impairs working memory in depression. The ability to shift set away and disengage from negative stimuli is also impaired due to a suppressed dorsolateral prefrontal cortex.

Increased access to emotional memory of negative valence occurs via an activated amygdala and hippocampus, with this being facilitated by both the significant hypercortisolemia (Gold et al., 1986) and the hypernoradrenergic drive (Gold et al., 2005).

Reduced subgenual anterior cingulate cortex regulation of the nucleus accumbens leads to anhedonia. Deep brain stimulation of the nucleus accumbens has also been shown to improve depression (Nauczyciel et al., 2013). Pessimistic outlook of depressed individuals is likely due to increased levels of the serotonin

transporter in the synapses, which decreases the amount of serotonin available for neurotransmission. There is evidence of increased serotonin transporter binding in pessimistic individuals (Disner et al., 2011).

### **Psychoendoneuroimmunological Responses**

#### **A. The HPA axis**

- i) **Role in the Normal Stress Response:** The subgenual anterior cingulate cortex suppresses the HPA axis and the sympathetic nervous system (Diorio et al., 1993). Stress causes reduced functioning of the subgenual anterior cingulate cortex, ‘releasing’ the corticotropin-releasing hormone (CRH) and sympathetic nervous systems, leading to the secretion of cortisol and noradrenaline. A stimulated amygdala also has similar effects (Phelps & LeDoux, 2005).

The HPA axis is stimulated by CRH. The locus coeruleus too is stimulated, and this promotes arousal (Ashton-Jomes, 2005). However, the thyroid, gonadal and growth hormones are suppressed by CRH, thus conserving energy during the stressed state. Other actions include reduction of sleep and appetite (Gold et al., 1988a; 1988b; Chrousos & Gold, 1992).

Cortisol plays several important functions during stress. It stimulates the amygdala, producing anxiety (Makino et al., 1994). It causes transient insulin resistance, increasing glucose availability for the brain. It also stimulates the renin-angiotensin system in anticipation of hypovolaemia which might result from bleeding during the fight-or-flight response (Gold et al., 2015).

- ii) **The Dysregulated Response That Contributes to Depression:** Increased CRH activity stimulates the HPA axis leading to hypercortisolism in depression and also activates the sympatho-medullary system and the locus coeruleus (see above). This results in the manifestation of the clinical picture of melancholic depression. On the contrary, there is evidence of decreased CRH function in atypical depression (Joseph-Vanderpool et al., 1991). Apart from the difference in neurovegetative symptoms between melancholic and atypical depression, other differences include an earlier onset, significantly greater occurrence of trauma during childhood and adolescence and higher frequency of chronicity in the case of atypical depression (Withers et al., 2013).

The hypercortisolism in depression has wide-ranging deleterious consequences

on physiological functioning including inhibition of gonadal, thyroid and growth hormones, inhibition of appetite, sleep and sexual behaviour, activation of amygdala, loss of hippocampal volume, inhibition of BDNF expression, neuronal apoptosis, toxicity to glial cells, insulin resistance, hypertension, visceral fat deposition, inhibition of thrombolysis and loss of bone mass (Gold et al, 2015).

## B. Stimulation of the Noradrenergic System

- i) **Role in The Normal Stress Response:** The locus coeruleus is a nucleus in the pons of the brainstem involved with the physiological responses to stress and panic, once it is activated by a stimulated amygdala. Brain synthesis of noradrenaline occurs in the locus coeruleus. It serves as an alarm system and reduces neurovegetative functions, for example eating or sleeping (Ashton Jones, 2005). Noradrenaline, in turn, stimulates the amygdala and inhibits the subgenual prefrontal cortex (Phelps & LeDoux, 2005). It facilitates the long-term storage and retrieval of emotional memories that possess a negative valence (McGaugh, 2004). Noradrenaline has a number of other effects on peripheral tissues, for example, the heart, vasculature, respiratory and gastrointestinal tracts, all of which prepare the stressed individual for fight or flight.
- ii) **The Dysregulated Response That Contributes to Depression:** The locus coeruleus– noradrenaline system as well as the CRH/HPA axis are stimulated by a disinhibited amygdala. A positive feedback loop is created whereby these in turn stimulate the amygdala, leading the amygdala to further suppress the subgenual prefrontal cortex. Also, the locus coeruleus–noradrenaline system and CRH/HPA stimulate one another. There is evidence of the hyperactivity in the locus-coeruleus-noradrenaline system, the sympathetic nervous system and adrenal medulla in severe melancholic depression – significantly high levels of noradrenaline have been found in the cerebro-spinal fluid (CSF) and plasma as have plasma adrenaline and plasma cortisol in such patients, when measured hourly over 24 hours (Gold et al., 2005).

## C. Monoaminergic system

- i) **Role in The Normal Stress Response:**

Noradrenergic activity during stress is as described above.

During a normal stress response, dopaminergic activity is moderately

decreased. Reduced serotonergic neurotransmission leads to a stressed state of the subgenual prefrontal cortex (Gold, 2015). Appropriate serotonergic neurotransmission is known to reduce the firing rate of the amygdala (Puig & Gulledge, 2011).

**ii) The Dysregulated Response That Contributes to Depression:**

- a) **Noradrenaline dysregulation in depression:** there is a noradrenergic overdrive in melancholic depression, in response to a disinhibited amygdala (Gold et al., 2005). A positive feedback mechanism causes the hyperactive noradrenergic state to, in turn, stimulate the amygdala which suppresses the subgenual prefrontal cortex further. Hence, increased activity of noradrenergic circuits is seen in the brain of individuals vulnerable to stress-induced depression (Saveanu & Nemeroff, 2012).

Postmortem of patients with MDD has shown increased density of  $\alpha_2$ -adrenergic autoreceptors in the locus coeruleus compared to controls (Ordway et al, 2003). This suggests reduced noradrenergic transmission in depression and noradrenaline (NA) reuptake inhibitors, for example, reboxetine, are known to be effective antidepressants (Saveanu & Nemeroff, 2012).

- b) **Serotonin dysregulation in depression:** reduced serotonin neurotransmission is thought to occur in depression. Coupled with decreased stimulation of 5-HT<sub>1a</sub> receptors, this leads to increased metabolic activity of the subgenual prefrontal cortex and increased firing of the amygdala (Gold, 2015). Decreased serotonergic neuronal activity in depressed patients has been demonstrated in CSF, neuroendocrine and postmortem studies (Saveanu & Nemeroff, 2012). An important finding implicates a faulty serotonergic system – those with the s allele of the promoter region of the serotonin transporter (SERT) gene (SLC 6A4) are highly vulnerable to depression following exposure to early life stress, such as child abuse (Caspi et al., 2003).

- c) **Dopamine (DA) dysregulation in depression:** reduced dopaminergic activity in depression causes anhedonia (see above). Evidence for decreased DA activity in depression includes the increased postsynaptic DA D<sub>2</sub>/D<sub>3</sub> receptor density (Saveanu & Nemeroff, 2012) as well as reduced DA transporter binding sites in postmortem and positron emission tomography (PET) studies (Meyer et al., 2001). Inadequate response to selective serotonin reuptake inhibitors (SSRIs)

and selective serotonin-noradrenaline reuptake inhibitors (SNRIs) is thought to occur due to their lack of effect on brain DA circuits (Dunlop & Nemeroff, 2007).

#### D. Glutamate system

- i) **Role in The Normal Stress Response:** Glutamate is an excitatory neurotransmitter. During a normal stress response, it stimulates the firing rate of neurons such as the CRH, locus coeruleus–noradrenaline and sympathetic nervous systems, and leads to adaptive neurogenesis and neuroplasticity (Gold, 2015).
- ii) **The Dysregulated Response That Contributes to Depression:** Acute stress causes glutamate release, while chronic stress leads to sustained increase in glutamate levels (Vale et al., 1981). Glutamate neurotoxicity results from excessive synaptic glutamate with resultant neuronal atrophy and loss of neuroplasticity and neurogenesis as well as eliciting a stress response at the endoplasmic reticulum. Excitotoxic damage due to excessive glutamate occurs in the prefrontal cortex and hippocampus in depression (Gold, 2015). Evidence shows that NMDA receptor antagonists reduce stress-induced atrophy of CA3-pyramidal neurons while the stress-induced loss of neuroplasticity in experimental animals is attenuated following administration of ketamine (an NMDA antagonist) (Duman & Li, 2012).

#### E. A pro-inflammatory, prothrombotic, insulin-resistant state

- i) **Role in The Normal Stress Response:** A pro-inflammatory state occurs during stress in anticipation of an injury that might occur during a fight-or-flight response. Cytokines, in addition to contributing to inflammation, have important actions in supporting the normal stress response by stimulating the CRH/HPA axis (Spinedi et al., 1992), the sympathetic nervous system (Papanicolaou et al., 1996), assisting insulin resistance (Hotamisligil et al., 1993), and activating the coagulation system (Joseph et al., 2002). Similarly, a prothrombotic state occurs in anticipation of likely bleeding during fight-or-flight. The insulin-resistant state enables delivery of sufficient glucose to the brain to meet its extra energy requirements while orchestrating the stress response.

- ii) **The Dysregulated Response That Contributes to Depression:** chronic stress

causes a chronic overactivity of the immune system, leading to sustained elevation of several inflammatory markers. There is consistent evidence of raised levels of proinflammatory cytokines, for example, interleukin 1 (IL-1), interleukin 6 (IL-6), interferon-gamma, tumour necrosis factor-alpha (TNF-alpha) and C-reactive protein (CRP, an acute phase protein) in depressed patients (Anisman et al., 2005; Schiepers et al., 2005; Lanquillon et al., 2000). Also, the level of cytokine elevation has been found to be directly correlated to the severity of depressive symptoms (Anisman et al., 1999; Mohr et al., 2001). Increased incidence of depression is known to occur in various inflammatory medical diseases, while inflammatory diseases such as cardiac disease and diabetes are known to occur at significantly higher rates in depressed individuals (Rudisch & Nemeroff, 2003). Anti-inflammatory agents such as celecoxib and etanercept have shown significant antidepressant effects (Muller et al., 2006; Tyring et al., 2006).

## **Neuro-Generative Responses**

### **A. Brain-derived neurotrophic factor**

- i) **Role in The Normal Stress Response:** BDNF plays a role not only in neurogenesis and neural stem cell differentiation, but also in the growth of axons, in neuronal differentiation into axons and dendrites, formation of synapses and neural circuit maturation (Park & Poo, 2013).

Exercising is a form of mild controllable stress that is known to have beneficial effects in depression due to raised BDNF actions. Increased BDNF actions are also known to occur with positive early childhood experiences. Chronic stress produces a couple of deleterious effects – there is greater expression of BDNF in the amygdala and lesser expression in the hippocampus (Gold, 2015).

- ii) **The Dysregulated Response That Contributes to Depression:** Hypercortisolism during stress states inhibits BDNF, while low BDNF levels cause cortisol levels to rise further – a vicious cycle (Gold, 2015). Chronic stress leads to a reduced expression of BDNF, likely reducing the volume of both the prefrontal cortex and the hippocampus in depression (Duman & Li, 2012; Autry & Monteggia, 2012). Antidepressants are known to block these effects of low BDNF levels (Duman & Li, 2012).

**B. Neuroplasticity**

- i) **Role in The Normal Stress Response:** Synaptogenesis increases during mild stress. This helps by enabling better information processing that might be required to deal with a stressful situation (Pittenger & Duman, 2008).
- ii) **The Dysregulated Response That Contributes to Depression:** Postmortem studies of deceased depressed patients have shown decreased dendritic branching and reduced neuronal spine density in the subgenual and dorsolateral prefrontal cortices as well as in the hippocampus. The amygdala, on the other hand, increases in size (Pittenger & Duman, 2008).

**C. Neurogenesis**

- i) **Role in The Normal Stress Response:** Neurogenesis enables a proper stress response to be mounted. It is associated with improved pattern recognition. This is pertinent in stressful situations as it can assist in recognition of threats. The hippocampal dentate gyrus and the subgranular zone of the lateral ventricles are the two sites of neurogenesis in adult brains (Duman & Li, 2012; Ming & Song, 2011; Gold, 2015). Neurogenesis is stimulated by mild stress of acute duration, a stimulating environment, long duration antidepressant therapy and exercise.
- ii) **The Dysregulated Response That Contributes to Depression:** increased cortisol levels (resulting from stress-induced HPA activation) reduce neurogenesis, on the other hand, neurogenesis blunts stress-induced cortisol secretion. Studies in rodents have shown that neurogenesis reduces significantly in response to chronic stress that produced depression-like manifestations. Administration of antidepressants led to appropriate neurogenesis in an animal study. It was found, however, that the antidepressant was ineffective if neurogenesis was thwarted (Santarelli et al., 2003).

**D. Epigenetic changes**

- i) **Role in The Normal Stress Response:** Epigenetic changes lead to heritable changes in gene expression due to mechanisms unrelated to any change in the DNA sequence (Saveanu & Nemeroff, 2012). These changes in gene expression switch genes on or off, and hence influence which proteins get synthesised. These changes are stress-induced and involved in neuronal plasticity and function (Simmons, 2008; Nestler, 2012). The epigenetic

modifications caused by early life stress include DNA methylation – the best characterized, with the other two being histone modifications and noncoding RNA-mediated regulation of gene expression (Simmons, 2008). Dealing with stress in adaptive ways is made possible by epigenetic changes (Gold, 2015).

- ii) **The Dysregulated Response That Contributes to Depression:** DNA methylation in the promoter region silences the gene. A postmortem study found methylation in the promoter region of the glucocorticoid receptor (GR) gene in the hippocampus of suicide victims who had been abused as children, but not in suicide victims without a history of child abuse. This methylation likely increases the stress response by silencing the GR gene (McGowan et al., 2009).

Evidence suggests that early life stress-induced epigenetic changes may be reversible. In an animal study, maternal deprivation in rats was used to induce stress and DNA methylation of the GR gene. Methionine, which modulates methylation, was given to these rats. The methionine caused demethylation and reversed stress responses in the rats (Weaver et al., 2005). Other animal studies have shown that prenatal stress leading to epigenetic alteration can be reversed by positive postnatal experiences (Dudley et al., 2011).

Hence, whether an individual who has faced adversity and stress will be prone to a stress-related psychiatric condition or be resistant to stress is dependent on gene-environment interactions that are influenced to an extent by epigenetic mechanisms. It is to environmental factors that we turn our attention to next.

## **PSYCHOSOCIAL MECHANISMS LINKING STRESS AND DEPRESSION**

### **The Meaning & Context of Stress is Important**

Stressful life events are an inevitable part of life. However, most people who experience stress do not become clinically depressed (Bruce, 2002). The mechanism which links psychosocial stressors to eventually developing depression has received extensive attention over the last four decades. Brown & Harris (1978) stated that stress *per se* was not as important in causing depression as the meaning that the stressed individual attributed to the stressor as well as the social context in which the stress occurred. For example, the stressor of divorce must be contextualised in

the broader social implications that are entailed, for instance, the availability of other forms of social support, financial dependency or otherwise, whether divorce is considered socially undesirable (as in certain cultures), etc. Further, in their ground-breaking work, Brown & Harris (1978) showed that for the stressor to be depressogenic, it should symbolise *loss* for the concerned individual. This loss could encompass a variety of scenarios such as the loss of status, relationship, material losses, etc. Further features of depressogenic stressors include the experience of entrapment and humiliation.

### **Early Life Stressors Can Leave Lasting Vulnerability**

Ample evidence has accumulated over the years demonstrating early childhood adversity raising the risk of depression into adulthood. In quantifiable terms, the risk was found to be raised by four times according to a review of the mental health consequences of early childhood abuse (Kendall-Tackett, 2002). Losing a mother before age 11 years has been found to be a risk factor for developing depression in adulthood, after suffering a significant life event. Examples of adverse childhood experiences that have been found associated with depression in adulthood include physical and sexual abuse and significant parental neglect (Brown, 2002).

### **Differential Exposure to Stressors & Higher Prevalence of Depression in Females**

Across cultures and nations, women have been found to have nearly twice the prevalence of clinical depression than men (Hammen, 2018). Hormonal differences between the sexes has been thought to be responsible for this difference in prevalence. Certainly, there is an inherent biological vulnerability to mood diathesis in women given the occurrence of conditions such as premenstrual dysphoric disorder and postpartum disorders exclusively in women. However, the majority of women do not experience these conditions in spite of sharing the same hormonal physiology as women who do suffer these mental health disorders (Martel, 2013; Steiner et al., 2003). Evidence suggests that there is a differential exposure to stressors, with girls in adolescence and women experiencing more stressors than men. These stressors may be in the form of child sex abuse or sexual abuse as adults and domestic violence (Barth et al, 2013; Stoltenborgh et al., 2015). Other stressors include disadvantaged social status, being poorer, having lesser power, and being burdened with chronically stressful roles (Hammen, 2018). Evidence suggests that women are more vulnerable to experience distress due to interpersonal issues and loss. This might occur due to women's tendencies to display greater nurturing behaviour than

men, which happens as a result of a combination of biological ‘hardwiring’ and cultural reasons (Cyranowski et al., 2000; Kendler & Gardner, 2014).

### **The Relation Between Stress and Depression is Bidirectional**

While it is known that stress leads to depression, there is evidence that a history of being depressed is associated with experiencing higher levels of stressful life events. In a longitudinal study, Hammen (1991) found that among unipolar depressed, bipolar, medically ill, and well women, negative events were found to be significantly higher in those with a history of unipolar depression compared to others. No difference was found in the frequency of independent life events experienced among the groups. However, the negative events that were significantly greater in frequency in the unipolar depressed group, were dependent events, in the sense that the individual had played a role in causing the event. Moreover, these events commonly occurred in the remitted state, and hence were not occurring due to an ongoing, current depressive episode. This phenomenon has been called stress generation (Hammen, 1991) and various subsequent studies in depressed or at-risk children, adolescents and adults have borne out this phenomenon (Hammen, 2006; Liu, 2013; Liu & Alloy, 2010). Stress generation, specifically interpersonal stress, also seems to be unique to depression (Conway et al., 2012).

There are several predictors of stress generation: a negative cognitive style (Safford et al., 2007), history of child abuse (Harkness et al., 2008), excessive reassurance seeking (Shih & Auerbach, 2010), neuroticism (high negative emotionality) (Stroud et al., 2015), genetic factors (Kendler et al., 1999) and gene-environment interactions (Harkness et al., 2015; Starr et al., 2012, 2014).

Stress generation has practical implications. A vicious cycle may be initiated once a depressed individual generates stress, which in turn can lead to depression, ensuring that the depression either turns chronic or else a recurring, relapsing pattern of depression ensues. Further, the interpersonal stress generated by the depressed individual may burden family and/or caregivers, producing problems in family and occupational spheres (Hammen, 2018).

### **The Kindling Phenomenon: The Initial Depressive Episode has a Stronger Association with a Stressor than later Episodes**

A stressor precipitates the initial mood episode in a vulnerable individual, however, subsequent mood episodes do not necessarily require the presence of a preceding

stressor (Post, 1992). It is now known that the kindling phenomenon also occurs in unipolar depression (Kendler et al., 2000; Monroe & Harkness, 2005; Stroud et al., 2011). It has been found that the level of stress required to precipitate a depressive episode is lower in individuals who were exposed to stressors as children (Hammen et al., 2000). Kindling likely occurs due to an interplay between genetic, cognitive, psychosocial and neurobiological factors and this is a subject of ongoing research (Hammen, 2018).

## TREATMENT CONSIDERATIONS

### A. PSYCHOTHERAPY

There is some evidence that psychotherapy is a crucial component of the management of chronic clinical depression in patients with a history of childhood trauma. A study conducted by Nemeroff et al., (2013) in this population found that among 681 patients treated with cognitive psychotherapy or nefazodone, or a combination of both, psychotherapy was superior to pharmacotherapy. Combination therapy was slightly superior to psychotherapy alone.

The main modalities of psychotherapy are considered below.

### COGNITIVE-BEHAVIOURAL THERAPY (CBT)

This treatment modality is based on the understanding that cognitive appraisals regarding stressful life events and subsequent coping are instrumental in how an individual responds to stress. The models of stress and coping developed by Lazarus & Folkman (1984) form the basis for stress management by CBT. This model states that two kinds of cognitive appraisal regarding the stressful situation are key to the stress response. *Primary appraisal* is the meaning the individual gives to the event. If the event is appraised as representing a loss, or as being harmful or threatening, anxiety, depression or withdrawal follows. If, however, the event is interpreted as being merely challenging, positive coping is possible. *Secondary appraisal* involves contemplating how the stressful event can be dealt with and whether this is likely to work.

CBT focuses on helping individuals raise their awareness about their own cognitive appraisals about stressful events. It further helps individuals understand how their appraisals affect their emotional and behavioural responses and how these appraisals may be modified leading to improved mental well-being. Detailed

treatment of the CBT approach to stress management training is beyond the scope of this chapter.

### **Psychodynamic Psychotherapy**

Psychodynamic psychotherapy retains relevance in this population due to its focus on the meaning of symptoms, conflict, developmental arrests, attachment and relationships. As Gabbard (2014) states: “a psychodynamic therapist would carefully evaluate the nature of the stressor that appeared to trigger a depression. Did the stressor involve humiliation and loss? Did it reawaken early childhood losses or traumas? What was the particular meaning of the stressor to the patient? ... Eventually, the therapist develops a formulation of the patient’s difficulties that involve both early developmental issues and the current situation. The meaning of the stressor will probably figure prominently in the formulation.”

From the above, we can appreciate that the meaning of the stressor holds significance in both the CBT as well as psychodynamic therapy approaches.

It has been suggested that psychotherapy can produce changes in gene expression, although the exact mechanism of this change is not known. Studies have found that psychodynamic psychotherapy led to normalization of the suppressed prefrontal cortex and a hyperactive amygdala-hippocampus in patients with panic disorder (Beutel et al., 2010). Another study found that patients who received short-term psychodynamic psychotherapy had a significant increase in density of 5-HT1A receptors on PET scan, compared to patients who received fluoxetine (Karlsson et al., 2010).

### **B. Pharmacotherapy**

It has been shown that while CBT improves the functioning of the prefrontal cortex, thus enabling better cognitive control, antidepressants act on the hyperactive amygdala (DeRubeis et al., 2008). Studies have demonstrated that neuroendocrine system dysregulation needs to be normalised to achieve remission. Treatment-responsive patients have shown significant reductions in CSF CRF on receiving treatment with electro-convulsive therapy and fluoxetine (Saveanu & Nemeroff., 2012).

Evidence from animal studies shows that SSRIs are able to reverse trauma-induced neurobiological effects (Gutman & Nemeroff., 2002). Treatment with

paroxetine led to reductions in raised levels of CNS CRF mRNA expression as also the high ACTH and corticosterone levels that were seen in adult rats who had experienced maternal deprivation (Huot et al., 2001).

Antidepressants help to normalise the dysregulated HPA axis and thus can act synergistically with psychotherapy in treating depression associated with childhood adversity.

## **CONCLUSIONS**

The normal stress response has evolved to mobilise and conserve resources to allow for effective coping with adverse situations. This normal response serves its purpose well while dealing with brief, controllable stress. Some of the mechanisms involved in a normal, effective stress response include the release of cortisol and noradrenaline, effective neuroplasticity, neurogenesis, epigenetic adaptations, and proper feedback regulation of biological processes. However, when this adaptive, normal response becomes dysregulated, either in the face of stress experienced at a critical development stage, or due to the chronic, uncontrollable nature of stress, this may lead to depression and a host of other physical ailments. Exposure to childhood adversity can lead to enhanced vulnerability to develop depression following further exposure to stressors in adulthood.

The suppression of the subgenual prefrontal cortex which results in disinhibition of the amygdala is key to the pathophysiology of the depression that ensues following exposure to stress. The meaning attributed to the stress by a particular individual has an enormous bearing on whether the stress will lead to negative mental health consequences for the individual. Previous life experiences influence the meaning the individual is likely to give to stressful, negative experiences.

Psychotherapy is of particular benefit in depressed individuals with a history of childhood trauma. Exploration of the meaning of previous trauma and current stressors, attachment, interpersonal issues, cognitive restructuring and emotional regulation are all pertinent. Pharmacotherapy helps with dampening a hyperactive amygdala and reversing epigenetic modifications wrought by trauma and stress. Psychosocial interventions that strengthen the support system are known to ameliorate the impact of early childhood adversity. Better understanding to the normal stress response will point the way to developing more effective therapeutic interventions for depression than the ones currently available.

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## **STRESS AND ANXIETY DISORDERS**

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### **OUTLINE**

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|----------------------------------|-------------------------------------|
| 1. INTRODUCTION                  | 2. STRESS MODELS OF ANXIETY         |
| 3. GENERALISED ANXIETY DISORDER  | 4. PANIC DISORDER                   |
| 5. SOCIAL ANXIETY DISORDER       | 6. SPECIFIC PHOBIA                  |
| 7. SEPARATION ANXIETY DISORDER   | 8. SELECTIVE MUTISM                 |
| 9. OBSESSIVE COMPULSIVE DISORDER | 10. MANAGEMENT OF ANXIETY DISORDERS |
| 11. CONCLUSIONS                  |                                     |

## **INTRODUCTION**

Anxiety disorders are one of the most common mental disorders and one of the leading causes of disability. It tends to start early in life and follows a chronic course if left untreated. The essential feature of anxiety disorder is excessive and enduring fear associated with avoidance behaviour. The underlying mechanisms leading to onset of anxiety disorder are poorly understood although genetic vulnerability, stressful life events and inhibited temperament have all been implicated as factors contributing to its onset. Given the amount of disability and impairment it causes, it is necessary to understand the various factors involved in the pathogenesis of anxiety disorders.

The word stress is derived from the French word “destresse” which means distress. Various forms of this word denote adversity. Walter Cannon, a Harvard physiologist, described the biomedical concept of stress as a reaction of our body’s resources to handle external threats in order to achieve homeostasis. Hence stress

is a complex interplay of events between our own body's fight/flight responses and external stimuli.

The role of stress in the genesis of anxiety disorders has been well known for decades. Anxiety disorders are possibly the result of adverse life events due to following reasons (Price,2003) a) It indicates possibility of repeated adversities in future b) It signals the body's incapability to handle stress – individual's vulnerability c) reduces one's capacity to handle further threats.

This chapter describes in detail about the association of stress with individual anxiety disorders.

## **STRESS MODELS OF ANXIETY**

Both stress and anxiety, in an evolutionary perspective, can be both adaptive and pathological. One must keep in mind that stress and anxiety can be either beneficial or harmful depending on their intensity; the point at which they turn from being beneficial to harmful is very blurred. Though psychiatrists and other mental health professionals emphasize more on treatment of anxiety at a disorder level, the evolutionary aspects should not be forgotten. This section describes the various models of stress and anxiety in general. Evidence of stress with specific anxiety disorders is highlighted in following sections.

### **Animal Models of Stress and Anxiety**

Early life stressful experiences such as maternal separation has been found to have long lasting consequences including generation of anxiety like behaviors in the experimental tests done in rodents(Lai et al., 2008). Stress induced by circadian rhythm changes and noise stimuli in experimental rats was also found to lead to anxiety related behaviors(Atkinson et al., 2006)(Naqvi et al., 2012). Exposure of chronic unpredictable stress in experimental animals found to increase HPA axis activity which further results in generation of anxiety behaviors(Mineur et al., 2006).

### **Neurocircuitry of Stress and Anxiety**

There is a significant overlap of neurocircuitry between stress and anxiety, indicating a link between the two. The activation of the limbic-Hypothalamus-Pituitary-Adrenal axis is relevant to both stress and anxiety (as explained later in this chapter). Major structures involved in this overlap includes subcortical

structures such as hypothalamus, hippocampus, amygdala, bed nucleus of stria terminalis and cortical structures such as insula and medial prefrontal cortex (Liberzon et al., 2007).

### **Neuroinflammatory Model of Stress and Anxiety**

Psychological stress has been found to increase the secretion of inflammatory cytokines. Pro-inflammatory cytokines such as TNF-alpha, IFN-gamma and IL-6 seem to increase proportionately with the level of stress severity. Stress induced anxiety is associated with increase in Th-1 like response and IFN-gamma and reduced IL-4 and IL-10 levels(Maes et al., 1998).

## **GENERALIZED ANXIETY DISORDER**

Generalized Anxiety Disorder (GAD) is one of the most common anxiety disorders across the world. The 12 month prevalence rate of GAD ranges from 0.4% to 3.6% across countries (American Psychiatric Association, 2013). According to National Mental Health Survey 2016 in India(NMHS Collaborators, 2016), the lifetime prevalence of GAD, among people aged above 18 years, is 0.57%. GAD can start at any age from childhood to late life, although it has been noted that the mean age of its onset is slightly later compared to other anxiety disorders (Wittchen et al., 1994).

The core feature of GAD is uncontrollable and excessive worry which is pervasive and affecting many spheres of life. The worry in GAD is usually associated with symptoms like muscle tension, restlessness, easy fatigability, difficulty in concentration, irritability and sleep disturbances (American Psychiatric Association, 2013). GAD, as an individual entity and as a comorbidity with other disorders like depression, contributes to a great degree of disability and impairment.

### **Link Between Stress and GAD**

The chronic or repeated psychological stress has been associated with various negative health consequences. The association between stress and incidence of GAD in future has not been widely studied. In following sections, we will review the available evidence on GAD and stress and some neurobiological underpinnings.

### **Early life stress**

Recent literature has demonstrated that early childhood adversities including early life stress has been associated with psychiatric morbidities in the future including

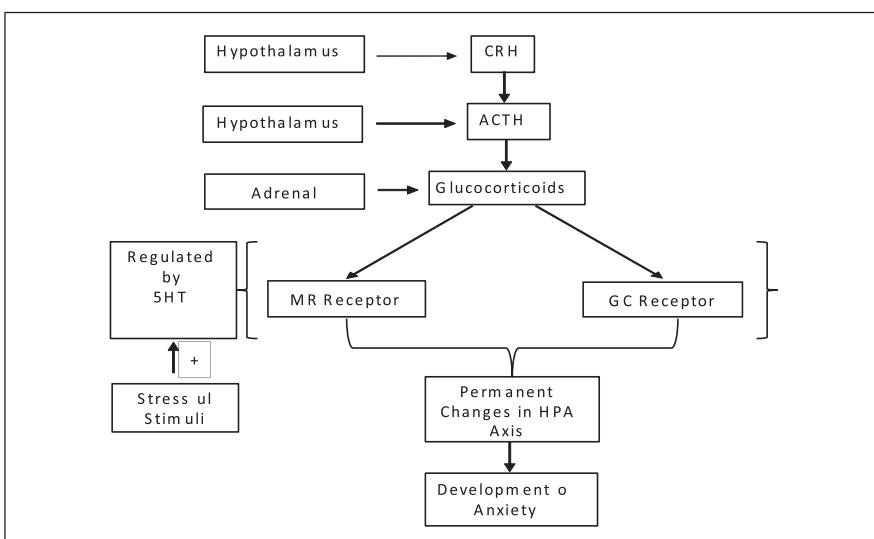
GAD. Early life stress is a broad term and includes traumatic experiences that occur during childhood and adolescence (Andreescu & Lee, 2020). Some of the examples of early life stress include parental loss/separation, deprivation of basic needs and childhood maltreatment. Childhood maltreatment can be divided into following sub-domains given in table 1 (Bernstein et al., 2003).

**Table 1: Childhood maltreatment**

Childhood maltreatment
Physical abuse – Physical aggression with risk or resulting injury
Emotional abuse – Verbal aggression that threatens, humiliates or affect the welfare of child
Sexual abuse – any sexual contact between a child and someone older
Emotional neglect – failure of caregivers to meet basic emotional needs such as love & support.
Physical neglect – Failure of caregivers to meet basic physical needs such as food, shelter and security.

One of the most consistent findings in link between early life stress and occurrence of anxiety disorders is alterations in Hypothalamo-Pituitary-Adrenal (HPA) axis. The following figure 1 illustrates the effect of stress on HPA axis and resulting anxiety disorder.

**Figure 1: HPA axis and Anxiety**



Studies have shown that early life stress leads to permanent changes in HPA axis and may lead to development of anxiety in later life. Most consistent findings in HPA axis alteration are increased activity of HPA axis leading to hypercortisolemia and decreased inhibitory feedback (Juruena et al., 2017) producing an adequate stress response, in this case, responding to hypoxia with an increase in hematopoietic stem and progenitor cells (HSPC). Evidence has shown that stress in early childhood can reduce the ability of HPA axis to respond to stress in later life and this can make a person susceptible to anxiety (Juruena et al., 2009). In patients of anxiety disorder if there is history of childhood trauma, they are likely to have poor response to pharmacological treatment and more likelihood of treatment resistance (Juruena et al., 2006).

### **Life events in adulthood**

Few studies have examined the association between stressful life events and onset of GAD. Among stressful life events, studies have taken dimensions of loss, danger, humiliation and entrapment. Among those dimensions, threat/danger was significantly associated with onset of GAD. Findings also show that onset of GAD was significantly predicted its onset with high threat events in the month of occurrence and also 3 months later (Finlay-Jones and Brown, 1981)(Kendler et al., 2003).

Under National Epidemiology Survey on Alcohol And Related conditions (NESARC) in U.S.A, a study was conducted to assess the relationship between adverse life events and onset of anxiety (Miloyan et al., 2018). This was the first population based study to assess the relationship between adverse life events and onset of anxiety disorder. Study findings show that around 69% of patients with GAD had at least 1 adverse life event. Table 2 illustrates the association between adverse event and onset of GAD.

Though there are few studies which have demonstrated the association between stress and GAD, the mechanism of causative role of stress has not been fully elucidated. Hence, more studies are required to establish consistent associations and also causative mechanisms involved.

**Table 2: Adverse events and Generalized Anxiety Disorder**

Adverse event	Onset of GAD (%) (n=1321)
Death of family or friend	35
Illness or injury of family or friend	46
Victim of crime	11
Financial crisis	25
Loss of job	7
Relationship failure	11
Any adverse event	69

## PANIC DISORDER

Panic disorder is a potentially disabling anxiety disorder, with chronic course and generally presents as comorbidity with other anxiety and depressive disorders. The 12 month prevalence rate of panic disorder ranges between 2-3% across countries (American Psychiatric Association, 2013). According to India's National Mental Health Survey 2016, the lifetime prevalence of panic disorder is 0.5%. Panic disorder peaks during adolescence, and its incidence is twice more common in females compared to males(American Psychiatric Association, 2013).

Panic disorder refers to recurrent, unexpected panic attacks(American Psychiatric Association, 2013). Due to its sudden nature and unpredictability, it can be threatening experience to patients leading to disability and increased health costs.

### Link Between Stress and Panic Disorder

The association between acute stress and onset of first panic attack has been documented in many studies. Also, recurrent stressful life events seem to alter the course and prognosis of panic disorder. Following section will review the evidence of association between panic disorder and stress and theoretical models associated with it.

### Early life stress

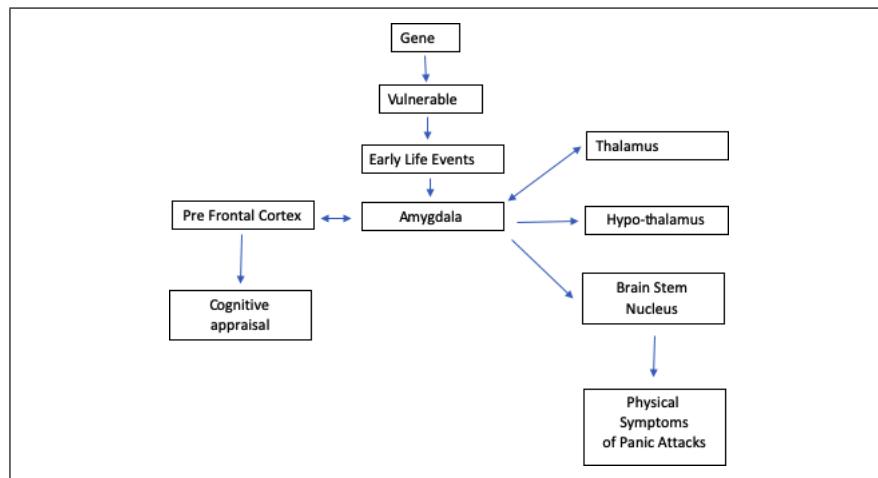
Childhood adversities have long been associated with occurrence of panic disorder. Specific life events in childhood have been studied to examine its association with panic disorder. There are some positive evidence showing association between

loss/separation with onset of panic disorder later in life (Bandelow et al., 2002). Further, these life events are associated with comorbid MDD and suicide attempts in patients with panic disorder (Servant and Parquet, 1994). However, there are some negative studies showing no association between loss/separation and panic disorder(David et al., 1995)(Jacobs & Bovasso, 2009).

There is a considerable good evidence on the impact of childhood abuse in the pathogenesis of panic disorder. One study has shown that the severity of childhood abuse proportionately increased the risk of developing PD (Young et al., 1997).

Gorman's neuroanatomical hypothesis of PD also talks about the significance of early life stressors in the pathogenesis of PD(Gorman et al., 2000). The following figure 2 illustrates the gene-environment interaction in the pathogenesis of PD based on Gorman's hypothesis.

**Figure 2: Neuroanatomical hypothesis of Panic Disorder**



### Life events in adulthood

Adverse life events have been regarded as candidate stressors in the occurrence of panic disorder. There is a considerably good evidence supporting the association between life events and incidence of PD. One study observed an increase in incidence of PD following a stressful life event (Faravelli & Pallanti, 1989) and another study observed an increase in stressful life events 2-3 months before occurrence of first panic attack (Faravelli, 1985). Using path modelling techniques,

one study described the direct effect of stressful life events in the onset of PD (Watanabe et al., 2005).

About 80% patients with panic disorder report at least one stressful life events 6 months before their initial panic attack (Uhde et al., 1985). Studies also describe cumulative effects of life events contributing to allostatic load in the occurrence of PD.

Specific life events have also been assessed for its association in PD. Interpersonal loss/conflicts has been consistently associated with incidence of PD. One study assessed the prevalence rate of PD in widowed individuals and found higher 6-month prevalence rate of PD in widowed individuals compared to controls (Jacobs et al., 1990). Another specific life event widely studied in PD is health related life event. An association between general medical illness such as migraine headache, CAD, mitral valve prolapse, thyroid disease, peptic ulcer disease and PD has been found (Härter et al., 2003). However, conclusions have to be drawn with caution regarding the causal nature of these medical illness in the onset of PD. There seems to be a bidirectional relationship between CAD and PD, some developing PD before CAD while some after CAD (Chignon et al., 1993) (Fleet et al., 2000). Table 3 illustrates the association between specific life events and onset of PD in a population based sample (Miloyan et al., 2018).

**Table 3: Specific life event and onset of Panic Disorder**

Adverse life event	Onset of PD (%) (n=964)
Death of family or friend	40
Illness of family or friend	44
Victim of crime	10
Financial crisis	25
Loss of job	10
Relationship failure	11
Any adverse event	71

Thus, there is definite association between stressors and PD quantitatively as well as qualitatively. However, one has to keep in mind that other factors such as genetic vulnerability and temperament factors such as negative affect and anxiety sensitivity also contribute to the pathogenesis of panic disorder.

## SOCIAL ANXIETY DISORDER (SAD)

Social anxiety disorder refers to the occurrence of marked or intense fear or anxiety of social situations in which individual may be evaluated by others (American Psychiatric Association, 2013). The 12- month prevalence rate of social anxiety disorder ranges from 0.5% to as much as 7% across the world (American Psychiatric Association, 2013). According to India's National Mental Health Survey 2016, the lifetime prevalence of social anxiety disorder is 0.47% (NMHS Collaborators, 2016).

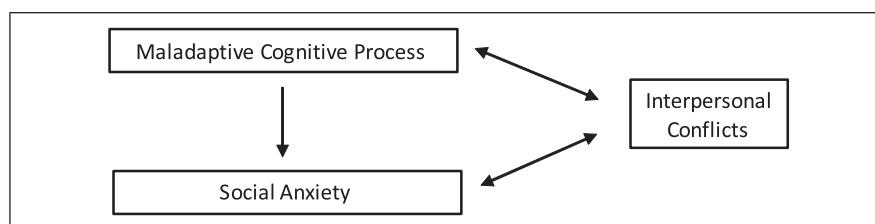
### Link Between Stress and SAD

Although most of the social anxiety models describe about maladaptive cognitive processes as having a central role in its development, role of stress is also gaining importance. Kendler, Thornton and Prescott distinguish between dependent and independent stress. Dependent stress is referred to stress generated by person's own behavior whereas independent stress as events beyond person's control (Kendler et al., 2001). Another differentiation is made between interpersonal stress (stress within relationships) and non-interpersonal stress(stress outside relationships) (Kendler et al., 2001). The role of stress in social anxiety, although scarce may be understood in terms of stress generation model. Dependent interpersonal stress may, especially, be associated with social anxiety (Hamilton et al., 2016)

The role of stress in SAD can be bidirectional. The occurrence of actual negative interpersonal events such as interpersonal conflicts can lead to maladaptive cognitive process in a vulnerable individual , while SAD can lead to interpersonal skill deficits (Siegel et al., 2018).

Figure 3 illustrates the role of interpersonal stress as a contributing factor in the development of SAD

**Figure 3: A model of Social Anxiety Disorder**



One study conducted in adolescents found that higher levels of social anxiety were significantly associated with negative interpersonal dependent events, even after taking into account for confounding variables (Siegel et al., 2018). Another study also found association between interpersonal chronic life stress and occurrence of SAD(Uliaszek et al., 2010).These studies also mention the bidirectional relationship between interpersonal stress and low extraversion to the contribution of SAD.

Hence, we can understand the clear need of more studies to elucidate the role of stress in the onset of SAD.

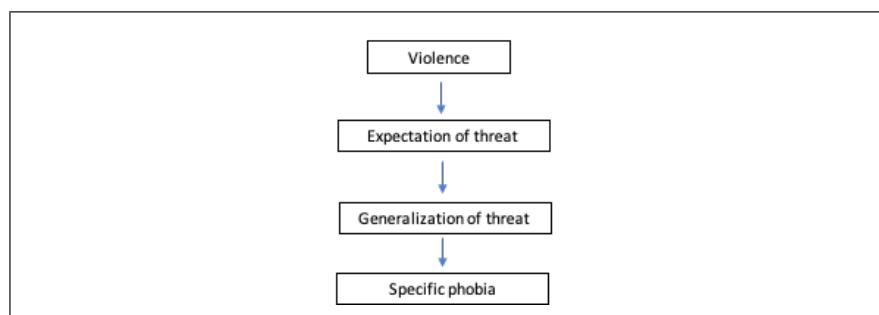
## SPECIFIC PHOBIA

Specific phobia refers to the development of fear or anxiety circumscribed to a particular object or situation called the phobic stimulus (American Psychiatric Association, 2013). The prevalence rates of specific phobia ranges between 2% -7% across countries. In India, the life time prevalence rate of specific phobia is 1.91% based on National Mental Health Survey 2016 (NMHS Collaborators, 2016).

### Link between stress and specific phobia

Theoretically, traumatic experiences have been expected to precipitate onset of specific phobia. However, studies have shown inconsistent results. One study has shown that early parental loss/separation was associated with specific phobia in one of the community sample(Tweed et al., 1989). Studies analyzing National Comorbidity Survey sample did not find any association between traumatic events and phobia onset (Green et al., 2010).

Figure 4: Social psychology model of specific phobia



Violence experienced in childhood has been shown to be associated with increased risk of specific phobia. Social psychology theory (figure 4) has attempted to explain the link between history of violence and occurrence of specific phobia. Constant threat of physical violence might cause individuals to expect harm and generalize it to other objects or situations(Magee,1999).

The following table 4 shows the frequency of association between adverse life event and onset of specific phobia (Miloyan *et al.*, 2018).

**Table 4: Adverse life event and onset of social phobia**

Adverse life event	Onset of specific phobia (n=2,252)
Death of family	35
Injury of family or friend	40
Victim of crime	6
Financial crisis	8
Loss of job	7
Relationship failure	8
Any adverse event	64

## **SEPARATION ANXIETY DISORDER**

Separation anxiety disorder is one of the common anxiety disorders in children. The core feature of separation anxiety disorder is characterized by the presence of excessive fear or anxiety in the context of separation from home or attachment figures (American Psychiatric Association, 2013). The 12 month prevalence rate of separation anxiety disorder in children is approximately 4% across countries(American Psychiatric Association, 2013). The prevalence of separation anxiety disorder in India is not well studied. There is a growing evidence about the occurrence of separation anxiety disorder even in adults. This has been reflected in the changes in DSM-5 which has included adults also in the diagnostic criteria.

Separation anxiety disorder has been recognized as a risk factor for other anxiety disorders in later life and a particular association has been noticed with panic disorder in adults (Lewinsohn *et al.*, 2008).

Though theoretically parental loss/separation is likely to precipitate separation anxiety disorder in children, such association has not been strongly found. The

parenting style and family environment are mostly studied in the pathogenesis of separation anxiety disorder(Orgilés et al., 2018). The role of stress in the pathogenesis of separation anxiety disorder has not been well studied.

## **SELECTIVE MUTISM**

Selective mutism is characterized by consistent failure to speak in specific situations where it is expected (American Psychiatric Association, 2013). The prevalence of selective mutism is not systematically studied. In a cross sectional study conducted at elementary school setting, the prevalence of selective mutism was estimated to be 0.03% to 2%(Karakaya *et al.*, 2008).

The etio-pathogenesis of selective mutism is poorly understood. Risk factors studied include parenting style, parental anxiety and temperament such as behavioral inhibition. Hence, currently we do not have any evidence for the role of stress in selective mutism.

## **OBSESSIVE-COMPULSIVE DISORDER**

Obsessive-compulsive disorder is a chronic illness characterized by repetitive intrusive obsessions, repetitive compulsions and avoidance. The prevalence of OCD ranges around 1-3%(Ruscio et al., 2010). According to National Mental Health Survey 2016 in India, the lifetime prevalence of OCD is 1.08%(NMHS Collaborators, 2016).

### **Link Between Stress and Obsessive-Compulsive Disorder**

Numerous environmental factors have been identified as risk factors in the development of OCD. Some of the factors include prenatal birth injuries, parental rearing styles, socioeconomic problems, trauma and so on. It can be understood using stress-diathesis model where complex interplay between stress and underlying vulnerability leads to the development of psychopathology (Zuckerman & Riskind, 2000). Early childhood adversity and childhood traumatic events are known to increase the risk of OCD (Lafleur et al., 2011). Neurobiologically, both acute and chronic stress seem to alter the balance in cortico-striato limbic circuits which is considered to be the main circuitry involved in OCD (Arnsten et al., 2017). Hence, stress play a significant role in the etiology and maintenance of OCD.

## MANAGEMENT OF ANXIETY DISORDERS

A comprehensive management of anxiety disorders is crucial as these are most common of the mental disorders which contribute to global burden of disease. Both pharmacological and psychological treatment has been shown to be effective in the treatment with its own limitations.

After the diagnosis of any anxiety disorder, a comprehensive assessment has to be conducted to evaluate the degree of distress and impairment, presence of any comorbid mental disorder, any medical illness and past response to treatment if any (National Institute for Clinical Excellence (NICE), 2011a). Educating patients about the nature of disorder and options of treatment has been gaining evidence as a part of management plan. The following section briefly reviews various treatment modalities in the management of anxiety disorders.

## PHARMACOLOGICAL MANAGEMENT

### Generalized anxiety disorder:

Pharmacological options in the treatment of GAD include Tricyclic antidepressants (TCA), Selective Serotonin Reuptake Inhibitors (SSRI), Selective Norepinephrine Reuptake Inhibitors (SNRI) and other novel agents.

National Institute for Health and Care Excellence (NICE) guidelines recommend a stepped care approach where a less intrusive yet effective intervention is selected first and can be stepped up with intensive treatment if no improvement is noted (National Institute for Clinical Excellence (NICE), 2011b). Benzodiazepines can be used for short term management and should be restricted for up to 4 weeks and for crisis intervention (Offidani *et al.*, 2013). Following table illustrates the current evidence in the pharmacological treatment in GAD as per NICE guidelines(National Institute for Clinical Excellence (NICE), 2011a).

**Table 5: Pharmacological treatment in GAD**

Drug	Comments
First line treatment (in order of preference)	Patient's preference to be taken into consideration
• SSRIs (up to maximum licensed dose)	Start at low dose and increase gradually.
• SNRIs (up to maximum licensed dose)	Start at low dose and increase gradually.
• Pregabalin (150-600 mg/d divided doses)	Response may start in first week (Generoso <i>et al.</i> , 2017)

Drug	Comments
Second line treatment (no order of preference)	
• TCAs – Imipramine (75-200 mg/d), Clomipramine (50-250 mg/d)	Poor tolerability
• Agomelatine (10-50 mg/d)	Some evidence in relapse prevention (Stein et al., 2012)
• MAOIs – Phenelzine 45-90 mg/d	Avoid food containing tyramine
• Betablockers – Propranolol 40-120 mg/d	Useful in somatic symptoms (Hayes and Schulz, 1987)
• Quetiapine 50-300 mg/d	Evidence as monotherapy
• Mirtazapine 15-30 mg/d	Good alternative option ,well tolerability (Gambi et al., 2005)
• Buspirone 15-60 mg/d	Late onset of action (Chessick et al., 2006)

### Panic disorder:

Pharmacological options in the treatment of panic disorder include SSRIs, SNRIs, TCAs, MAOIs and benzodiazepines. Though Benzodiazepines provide rapid relief from panic symptoms, effects are short lasting, and one should not forget the risk of abuse potential.

The choice of drugs can be made based on efficacy, tolerability, patient's profile as well as patient preference. The following table illustrates the drug options in panic disorder based on NICE guidelines(National Institute for Clinical Excellence (NICE), 2011b).

Table 6: Pharmacological treatment in Panic Disorder

Drug	Comment
First line treatment	
• SSRIs (up to maximum dose)	Initial exacerbation of panic symptoms might occur
• Venlafaxine (75-225 mg/d)	
Second line treatment	
• Mirtazapine (15-60 mg/d)	Good tolerability
• TCAs – Imipramine, clomipramine, Desipramine, Lofepramine	Start at low dose and increase gradually
• MAOIs Phenelzine 10-60 mg/d	Poor tolerability, not a preferred one

### **Social anxiety disorder:**

Pharmacological options in the management of social anxiety disorder has been illustrated below (Table 7)

**Table 7: Pharmacological management of social anxiety disorder**

Drug	Comment
<b>First line treatment</b>	
• SSRIs	
• Venlafaxine (75-225 mg/d)	
<b>Second line treatment</b>	
• Olanzapine 5-20 mg/d(Blanco et al., 2013)	Other antipsychotics less studied.
• Beta blockers	Reduces autonomic symptoms in performance situations
• Gabapentin 900 -3600mg/d (Blanco et al., 2013)	
• Pregabalin 150-600 mg/d	
• MAOIs Phenelzine 15-90 mg/d	Avoid food containing tyramine
• Benzodiazepines	Can be used in sos basis.

### **Psychological Management**

All patients with anxiety disorders require supportive therapy and psychoeducation. Psychoeducation includes explaining the nature of illness, need for treatment and various treatment options (drugs vs therapy). Various schools of psychotherapy have been studied in the management of anxiety disorders and CBT (Cognitive Behavioral Therapy) stands out from the rest in terms of evidence. In this section, we will review some of the psychological treatment available for anxiety disorders.

### **CBT for anxiety disorders:**

Cognitive behavioral therapy has been widely recognized as an effective treatment in the management of anxiety disorders. Two approaches are widely used – Exposure therapy and cognitive therapy.

### **Exposure therapy:**

Exposure therapy is one of the commonly preferred techniques in the treatment of many anxiety disorders. It is based on the principle of emotional processing theory (Foa and Kozak, 1986).In this, fear is described as result of associative networks that has information about feared stimulus, feared response and meaning of stimuli

and response. So, when an external/internal stimulus resembles any of the structure, the associative network is activated, and generation of anxiety occurs.

In exposure therapy, conditioned activation of fear structure is done to modify the unrealistic associations by disconfirming it. Exposure can take several forms – interoceptive, in vivo and imaginal, can be tailor made based on symptom nature. For example, interoceptive exposure is used in patients with panic disorder where physical sensations associated with fear are deliberately induced and attempted to modify the fear structure.

Exposure therapy tends to have a similar function in all anxiety disorders viz modification of fear structure but content of it might vary depending on the type of anxiety. Exposure therapy has been proved to be efficacious in many forms of pathological anxiety.

### **Cognitive therapy:**

Cognitive therapy is another widely employed method of CBT in the treatment of anxiety disorders. Cognitive therapy is based on Beck's triangle model of interrelation of thoughts, feelings and behavior. Identifying maladaptive thoughts (cognitive distortions) and cognitive restructuring is the core of cognitive therapy (Resick et al., 2010). Cognitive therapy can be used in conjunction with other behavioral techniques such as exposure exercises.

### **Applied relaxation training:**

Applied relaxation has been used as one of the treatment approaches in anxiety disorders. Though it has not been widely recognized as CBT, there are some evidences to support its efficacy comparable to CBT. Most popular technique among applied relaxation is progressive muscle relaxation, described by Jacobson in early 1930s. Progressive muscle relaxation involves tightening a muscle group followed by releasing with tension. Several modifications have also been described by various authors. One such modification is the technique of systematic desensitization which is widely used in specific phobias. Other stress management techniques such as deep breathing, ABC relaxation are also been tried in the management of anxiety(Paul & Shannon, 1966).

### **Other psychotherapies:**

Other forms of psychotherapy such as psychodynamic psychotherapy, Interpersonal

therapy, mindfulness-based meditation has also been employed in the management of anxiety disorders.

### **Complementary and Alternative medicine:**

Many individuals resort to non-pharmacological methods for alleviation of anxiety. Methods such as exercise and yoga are gaining popularity. This section briefly reviews the evidence on these options in management of anxiety.

### **EXERCISES**

Physical exercise such as aerobic and nonaerobic exercises have been tried for anxiety symptoms. It has been used as a standalone treatment for mild anxiety and in conjunction with other treatment (SSRIs or CBT) for moderate to severe anxiety. Meta-analysis of RCTs show that CBT or SSRIs are superior to exercise, however there are methodological limitations in quantification and qualification of various exercise methods (Stonerock *et al.*, 2015) but few studies have studied exercise in individuals preselected because of their high anxiety. Purpose: The objective of this study is to review and critically evaluate studies of exercise training in adults with either high levels of anxiety or an anxiety disorder. Methods: We conducted a systematic review of randomized clinical trials (RCTs). As exercise does not cause any harm and has other physical benefits, it can be safely recommended in patients with anxiety as an add-on treatment.

### **YOGA**

Evidence for yoga in the treatment for anxiety is currently less. Most studies have used Hatha yoga and frequency and duration of sessions is yet to be clear. Meta-analysis of yoga in patients with anxiety show that there may be modest benefit from yoga and hence preferred as an adjunctive treatment ( Hofmann *et al.*, 2016).

### **CONCLUSIONS**

The role of stress in the pathophysiology of anxiety disorders has been well known. There exists a bidirectional relationship between stress and anxiety which seems to under-estimated. The implications of stress in the causation and prognosis of anxiety disorders emphasizes the need to incorporate it in the management. The prevention of stressful life events such as childhood adversities has to gain importance both at clinical and at policy level.

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## **STRESS AND SLEEP DISORDERS**

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## **INTRODUCTION**

Stress is ubiquitous in our life. In layman terms, stress can be physical as we feel during exercise or can be emotional as we experience during demanding or competing situations. However, emotional stress is likely to exert multiple effects on the body. It is known fact that emotional stress can change behavior, cognition and feelings. In addition, it brings changes in functioning of other systems of the body viz., cardiovascular, endocrinial, respiratory, gastrointestinal, musculoskeletal and genitourinary. Changes in sleep, appetite and libido are well known during emotional stress. Changes in physiological functioning of body and central nervous system are brought about through a myriad of mechanisms that include activation of hypothalamo-pituitary-axis, initiation of inflammatory cascade and change in neurotransmission. In this chapter changes in sleep-pattern and sleep duration will

be discussed that are observed during stress. In addition, measures to be taken to reinstate the normal functioning of sleep-wake cycle will be discussed.

## DEFINING STRESS

Stress is the physiological response of the body towards a stressor. It is the fear, flight and fight reaction of the body. Stressors are seen by the human body as their environment changing objects which alter the homeostasis. The *Merriam-Webster's Dictionary AND Thesaurus (2014)* defines stress as “a physical, chemical, or emotional factor that causes bodily or mental tension and may be a factor in disease causation.” Stress is a term commonly used in day to day life and defining it precisely and scientifically is challenging. Historically, it is being used literally as a noun and verb in European languages, French, etc. for many centuries. It factually means “hardship”, “pressure” or “force” and has been used to define “a physical force which burdens an object”. Dietmar Kültz in 2020, have tried to define stress based on the principles of physics (Kültz, 2020). As per this article “*Stress is the sum of opposing forces that act on each physiological and morphological variable (trait) of cells and organisms.*” The term stress was coined by Selye H in 1965, and defined it as “*non-specific responses of the body to any demand for change*” (Selye, 1965).

Stress can be defined as one having negative emotional impact in form of biochemical, physiological and behavioral alteration in an individual (Baum, 1990). In simple words, stress can be understood as the body’s response to stressors which produce strenuous demands. Lazarus RS and Selye H submitted that there is positive as well as negative stress and have good (eustress) and deleterious (distress) implications on the body (Lazarus, 1996; Selye, 1975). As per the Yerkes-Dodson Law, stress was theorized to be very favorable and necessity for an optimal performance, however, after the limits are crossed the performance starts dropping (Benson & Allen, 1979).

The physical, mental or emotional stimuli which may change the body environment are deliberated as stressors by a body, and in order to achieve the homeostasis the sympathetic (sympathoadrenal medullary) and parasympathetic systems (hypothalamic–pituitary–adrenal axis) play the most crucial roles. The presence of stressors leads to activation of Autonomic Nervous System (Sympathetic Nervous System and Parasympathetic Nervous System) to produce varied physiological responses. The sympathoadrenal medullary axis (SMA)

regulates the fear-fight-flight response and the hypothalamic–pituitary–adrenal axis (HPA) involving pituitary, hypothalamus and adrenal modulates release of cortisol in order to cope with the stress. Dysregulation caused by the stress and inability to achieve homeostasis may lead to varied degrees of mental illnesses (Stephens & Wand, 2012). Alterations caused in this hormonal response system (HPA) by the stress has been evident clearly for decades in causing sleep related problems (Chrousos et al., 2000). Weitzman et al. in 1983, reported that deep sleep has negative influence on the HPA axis and on the release of cortisol (Weitzman et al., 1983).

## NEUROBIOLOGY OF STRESS

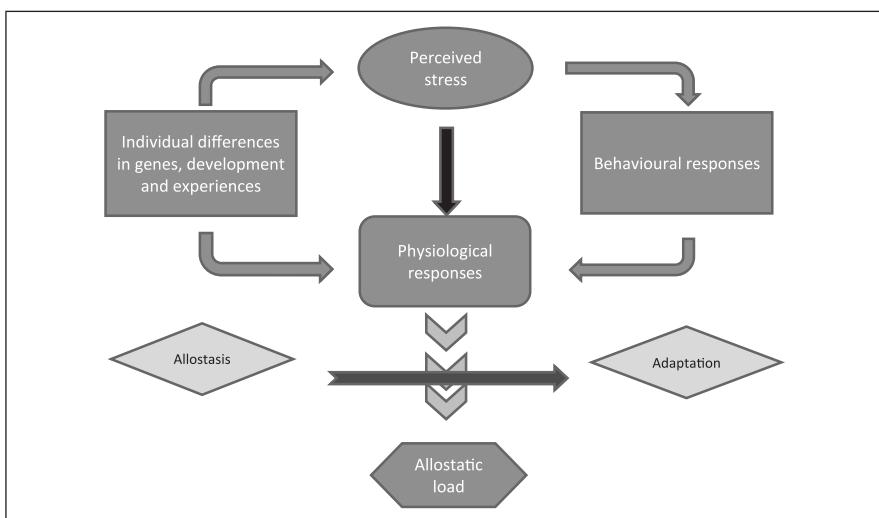
Considering the fact that we have already defined what *stress* is, let us classify it further into good stress, tolerable stress and toxic stress. The '*good stress*' is that in which a person faces a stiff challenge, equals to the task, takes risk for that, and gets rewarded by mostly a positive outcome, or rarely, an adverse outcome. The '*tolerable stress*' would imply a situation where a person having healthy brain architecture is able to cope in the face of adverse events, with the help of family, friends and other acquaintances. The '*toxic stress*' would mean that the person would be mostly unable to cope with the bad situation, because of limited supports, or a brain architecture, which reflects early adverse life events. Good stress is often synonymously known as *eustress*, whereas the uncomfortable feeling in both tolerable and toxic stress may be referred to as *distress*; the nature and degree of which may vary according to the ability to control the situation.

Two terms deserve special mention – *Allostasis* and *Allostatic Load*. The former refers to maintaining equilibrium at times of stress with the help of the sympathetic and parasympathetic systems, hypothalamic–pituitary–adrenal (HPA) axis, immune system and various other metabolic hormones and molecular processes. Allostatic load or overload would mean the wear and tear of the brain and body caused by the overuse or underuse of these systems and would thus promote pathophysiological mechanisms.

Hippocampus has been found playing a key role in memory and mood regulation. It is pivotal for spatial, episodic and contextual memory formation (Eichenbaum & Otto, 1992). Dendritic shrinkage and dendritic spine loss has been found to be effected by stress and glucocorticoids (McEwen, 2016). The hippocampus also plays a role in shutting off the HPA stress response, and hippocampal damage results

in impairment of this shut off, thus leading to a more prolonged HPA response to psychological stressors (Herman & Cullinan, 1997)). This progressive hippocampal damage and faulty negative feedback of glucocorticoids with increasing age and stressors, has been documented in the ‘Glucocorticoid Cascade Hypothesis’ (Conrad, 2008). Apart from this, protein hormones like IGF-1, insulin, ghrelin and leptin have receptors in the hippocampus. IGF-1 has been found to be involved in neurogenesis in the dentate gyrus (Carro et al., 2000) whereas ghrelin has been found to increase synapse formation in the hippocampal pyramidal neurons (Diano et al., 2006).

**Figure 1: Pivotal role of the brain in allostasis and adaptation.**



Glutamate is the major excitatory neurotransmitter, but excess of it, released during stress, causes inflammation and damage. Dendritic shrinkage due to chronic stress also occurs in medial amygdala and medial PFC. However, dendrites in basolateral amygdala and OFC expand in chronic stress (Chattarji et al., 2015). BLA may be considered as the seat of coding emotional valence in humans. If we consider the neurons of BLA synapsing in the core section of the NAc, majority of them would support reward seeking, whereas major population of neurons of BLA projecting to the CeA would mediate place avoidance or predict an aversive outcome (Namburi et al., 2015). While these two refers to the set of neurons dealing with learned emotional valence, neurons of the BLA projecting to the vHPC generates innate emotional states or anxiety (Felix-Ortiz et al., 2013).

## NEUROBIOLOGY OF SLEEP

Sleep is one of the basic needs of almost all animals, and humans are no exception, who tend to indulge in this for about one-third of their lives. With new tools and methodologies available, researchers have tried to unravel sleep architectures and their mechanisms from electrophysiological and molecular point of view. Let us first understand the three essential features of sleep – 1) rapidly reversible behavioural quiescence, which is not found in states like coma, seizure and hibernation; 2) reduced responsiveness to environmental stimuli; 3) homeostatic regulation, which enables the body to compensate later against any deviation done earlier (Joiner, 2016).

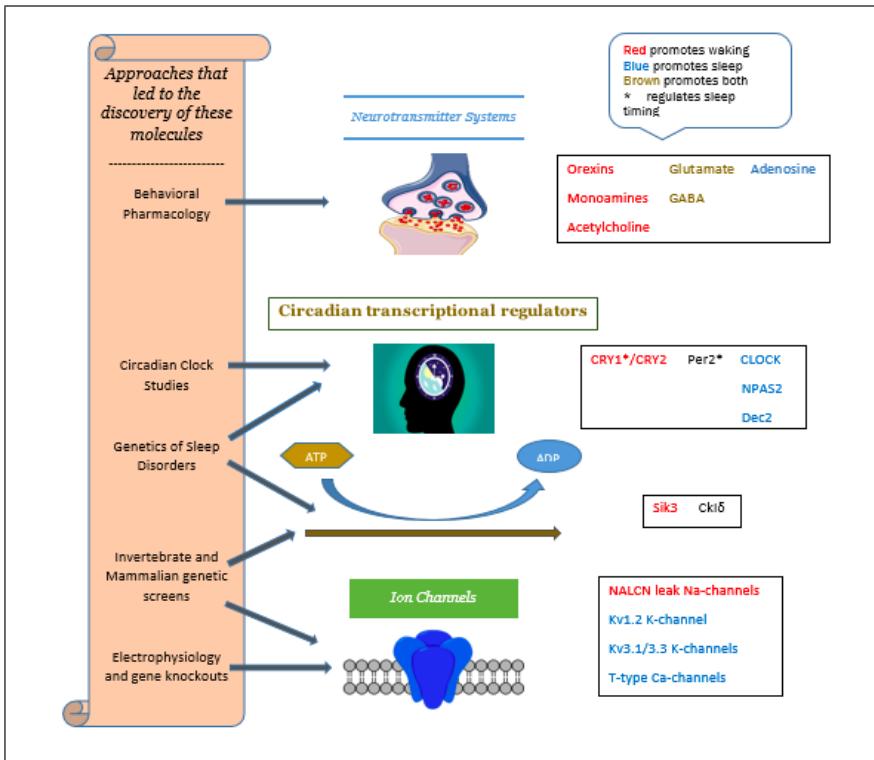
Electroencephalogram (EEG) dependent researches inferred that there are two internally driven processes – Process S which is sleep dependent, and Process C, which is sleep independent circadian process – playing pivotal role in sleep regulation (Borbély, 1982). Process S seems to increase during wakefulness and culminates with initiation of sleep; thus can be termed as the homeostatic sleep promoting process. On the other hand, Process C promotes wakefulness. This is achieved when the master clock, SCN of the hypothalamus, receives photic input from the retina and regulates brain regions directly and indirectly, thus maintaining wakefulness.

Wakefulness is also maintained by an additional brainstem locus – ARAS, which consists of dorsal raphe, the locus coeruleus, the ventral tegmental area, the laterodorsal tegmental nuclei and the pedunculopontine nuclei, releasing serotonin, noradrenaline, dopamine, and acetylcholine, respectively (Saper et al., 2005). These nuclei project through **dorsal** and **ventral** pathways to thalamus and basal forebrain respectively, which ultimately leads to the cortex.

Now let us understand what happens in each gross sleep stages. During awake state, the aforementioned cholinergic and monoaminergic nuclei activates both the pathways; the cortex remain excited, and the thalamus (due to dorsal pathway activation) does not filter out external cues, thus maintaining the wakefulness. In REM sleep, ventral pathway stimulation is continued by cholinergic nuclei resulting in cortical excitation; however the dorsal one is reduced by the monoaminergic neurons, thus enabling the thalamus to filter out sensory signals. This selective cholinergic activation also ultimately inhibits motor neurons in the spinal cord producing the diminished muscle tone observed during REM sleep. NREM sleep

necessitates reduction in stimulation of both the pathways, thus ensuring more sensory signal filtering at thalamus and a much reduced cortical activation (Joiner, 2016; Fraigne et al., 2015). Suppression of arousal is carried out by GABAergic neurons of the medulla oblongata (Anaclet et al., 2012), VLPO (Alam et al., 2014), subthalamus (Liu et al., 2017), and basal forebrain (Xu et al., 2015).

**Figure 2: Endogenous molecules that impact sleep**



Let us take a peek into the other neurochemical mediators involved in the control of sleep. A number of lymphokines, such as, IL-1, IL-6, TNF-alpha, and other inflammatory molecules and growth factors have been found to promote NREM sleep (Majde & Krueger, 2005). Neuropeptides like CRF and ACTH, both components of HPA axis, promote wakefulness (Ehlers et al., 1986). Intravenous NPY has been found to reduce sleep latency in young men (Antonijevic et al., 2000). MCH neurons have been implicated by optogenetic studies to have control over REM sleep (Tsunematsu et al., 2014) as well as sleep onset (Konadhode et al., 2013). Adenosine has been demarcated to play an important role as an endogenous

regulator of sleep and waking in the brain (Strecker et al., 2000). In the basal forebrain, Adenosine influences sleep homeostasis. Extracellular adenosine level rises with more time spent in wakefulness and lowers with recovery sleep, mostly in the basal forebrain and cortex (Porkka-Heiskanen et al., 2000). Astrocytes may be an important source of adenosine during waking, thus implicating the glial-neuronal interactions to play a role in sleep homeostasis (Schmitt et al., 2012).

Prostaglandin D2 has been found to act at sleep-promoting zone (PGD2-SZ), which is located outside the brain parenchyma, on the ventral surface of the rostral basal forebrain (Matsumura et al., 1994). Its CSF level has been found to increase in rats during sleep deprivation. PGD synthase (enzyme responsible for PGD2 synthesis) inhibition suppresses sleep and blockade of PGD2 receptors inhibits sleep (Takahata et al., 1993). When selective adenosine A<sub>2a</sub>-R agonist (CGS21680) is administered to the PGD2-SZ (not the selective adenosine A<sub>1</sub>-R agonist cyclohexyladenosine), it markedly induces sleep (Satoh et al., 1996). Thus PGD2 may be hypothesized to be coupled with A<sub>2a</sub>-R adenosinergic signalling via the brain parenchyma and that the PGD<sub>2</sub>-SZ plays an important role as an interface between these two systems. Melatonin, produced from the pineal gland is well known to induce sleep. Most of its receptors are found in cortex, suprachiasmatic nucleus, and hypothalamic regions involved in thermoregulation. Although photic stimulation influences melatonin production to some extent, it helps synchronize circadian rhythms in absolutely blind individuals (Lewy, 2007).

Hypocretins 1 and 2 (Hcrt), which are also termed as Orexins A and B, are a group of excitatory neuropeptides, almost entirely found in Posterior Lateral Hypothalamus (de Lecea et al., 1998), has been strongly associated with wakefulness. This association has been reinforced with measurements by Fos expression, electrophysiology, or brain/CSF peptide content (Estabrooke et al., 2001; Takahashi et al., 2008; Kiyashchenko et al., 2002). Clinically speaking, in narcolepsy, minimal amount of Hcrt1 has been found in CSF (Nishino et al., 2000). Absence of *prepro-hcrt* mRNA and about a 90% reduction in the quantity of Hcrt-containing cells in human narcoleptic brains, without an alteration in either MCH mRNA or the number of MCH cells, has been shown by postmortem studies (Peyron et al., 2000; Thannickal et al., 2000).

If we look at the circadian clock studies, it is good to know at the outset that there are two transcription factors, CLOCK (and its homologue NPAS2) and

BMAL, which the circadian oscillator utilizes and which heterodimerize to activate transcription of clock-controlled genes (DeBruyne et al., 2007). The *Period* (*Per*) and *Cryptochrome* (*Cry*) translation products heterodimerize as PER::CRY to repress CLOCK/NPAS2::BMAL1, and this loop has a negative feedback, which results in peaks and valleys of CLOCK/NPAS2::BMAL1 activity and therefore cycling transcription of clock-controlled genes, including *Per* and *Cry* (Takahashi, 2017). A second loop also exists, where CLOCK/NPAS2::BMAL1 upregulate transcription of *Ror* and *Rev-erb α/β*, which feedback to maintain appropriate transcription of the two factors, CLOCK & BMAL (Hirano et al., 2016). It should also be known that knockout of CLOCK/NPAS2 causes sleep decrement (Franken et al., 2006), while knockout of both CRY1 and CRY 2 causes increase in sleep (Wisor et al., 2002). Thus the coordinated function of all these molecules leads to transcriptional cycling of downstream effector genes over a period of ~24 hours.

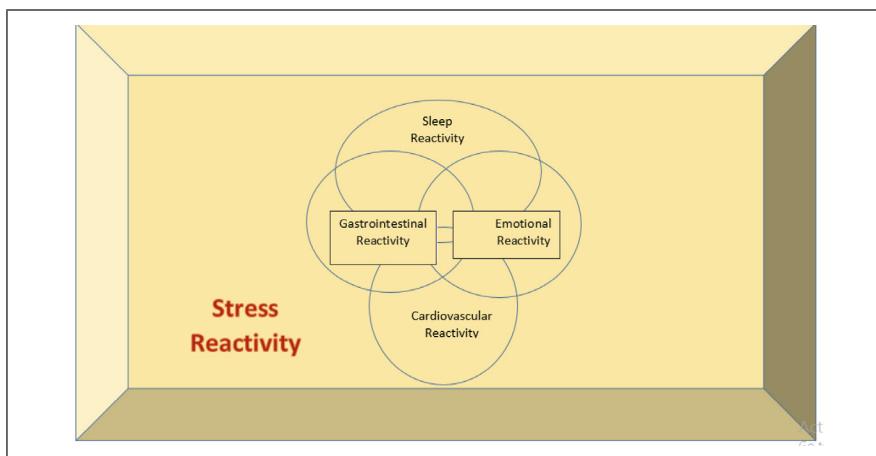
Let us look at some clinical implications. In the familial variety of DSWPD, a gain of function mutation in the core circadian clock gene *Cry 1* causes its translation product to constitutively repress CLOCK and BMAL1; thus, explaining the delay in onset of sleep (Patke et al., 2017). Contrastingly, in familial ASWPD, the earlier onset of sleep may be explained by the loss of function mutations in another core circadian repressor, *Per2*, and in a kinase that controls PER2's stability called CKI $\delta$  (Hallows et al., 2013). Electrophysiological studies have reported that ion channels like T-type calcium channels and Kv3-type potassium channels are required for burst firing of thalamic neurons that result in brain oscillations during NREM sleep (Astori et al., 2011; Espinosa et al., 2008).

## OVERLAP BETWEEN NEUROBIOLOGY OF SLEEP AND STRESS

Insomnia may occur in the background of a predisposition towards poor sleep and wake promoting hyperarousal; but stressful life events often act as a trigger and cognitive emotionally induced hyperarousal interferes with sleep and results in chronic insomnia in many people (Drake et al., 2013). On the other hand, patients having insomnia show exaggerated neurobiological and cognitive emotional reactivity to stress (Baglioni et al., 2010). *Situational insomnia* is a term assigned to the degree to which stress reactivity manifests in the sleep system. Synonymously, a term *Sleep reactivity* is being used to denote the degree to which a stressor disrupts or impairs sleep (Bonnet & Arand, 2003). Like most other traits, human beings

vary in having low to high sleep reactivity. Sleep reactivity is just one of the many components of stress reactivity as given in figure 3.

**Figure 3: Theorized relation of sleep reactivity to other components of stress reactivity**



Looking at the other side, total sleep deprivation of a single night has been found to induce generalized hyperalgesia and elevate state anxiety in healthy people (Schuh-Hofer et al., 2013). Similarly, sleep curtailment has been found to impair endogenous nociceptive-inhibitory function and increase spontaneous pain in healthy people (Smith et al., 2007). These suggest that the sleep disruptions not only perpetuate CNS hyperexcitability in people with chronic pain, but also may act as the causative factor. As poor sleep tends to reduce pain threshold, facilitating hyperalgesia, and because we have already known the effects of stressor/pain on sleep; this may actually turn into a vicious cycle.

If we look into the neurobiological correlates, atrophy of the mPFC, the hippocampus, and the ACC has been reported in people with chronic pain (Barad et al., 2014), while decrease in PFC size and atrophy of hippocampal structures have also been noted in people with insomnia (Reimann et al., 2007; Spiegelhalder et al., 2013). Heightened activities of the limbic areas has been found in patients having chronic pain as well as insomnia (Spiegelhalder et al., 2013; Strigo et al., 2008). Chronic pain and stressors are both known to dysregulate and activate the HPA axis; also raising the ACTH concentrations and altering the cortisol levels (Taylor et al., 1998). In a parallel manner, SWS has been found to reduce cortisol levels; whereas

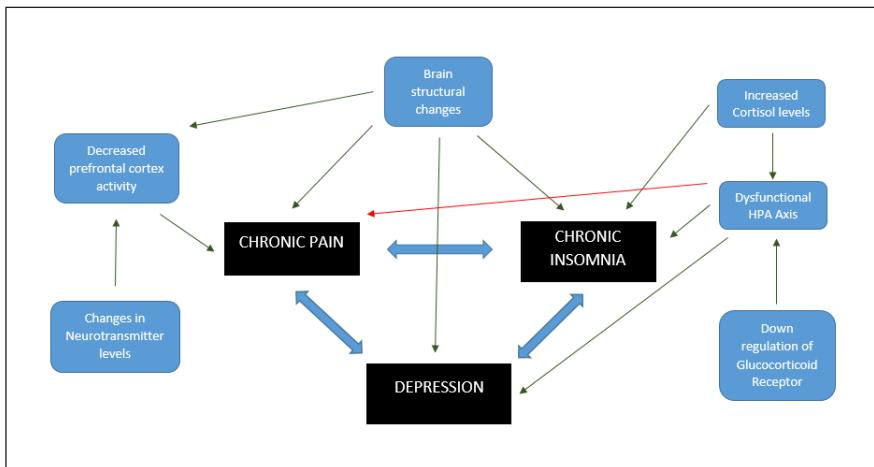
sleep deprivation increases it, thus activating the HPA axis (Born et al., 1986). BDNF is one factor which has been found to increase, mediated through a channel of signaling cascades, in neuropathic pain (Ulmann et al., 2008). It is thought to be increasing the excitability of 2<sup>nd</sup> order neurons in the spinal dorsal horn, leading to *central sensitization*, ultimately resulting in allodynia and hyperalgesia (DeLeo et al., 1997; Latremoliere & Woolf, 2009). However, in inflammatory pain, it has been found to be decreased in the hippocampus (Duric, V & McCarson, 2006). BDNF protein and its mRNA shows elevated levels during nonselective sleep, only in the hippocampus, which normalizes with sleep recovery (Fujihara et al., 2003). Thus it is understood that BDNF promotes sleep, as evident from other studies as well (Steiger, A & Holsboer, 1997). BDNF thus involves both the pain and insomnia pathways, as decrease of BDNF in the hippocampus in painful states could result in disturbed promotion of sleep.

Proinflammatory mediators, especially TNF, IL1 and IL6, released by activated immune and glial states, have been implicated in chronic pain (Scholz & Woolf, 2007). They trigger the development of persistent pain by causing axonal damage and modulating spontaneous nociceptor activity and stimulus sensitivity (Marchand et al., 2005), and are also responsible for allodynia and hyperalgesia in the dorsal horn (DeLeo et al., 1997). Although the mechanisms are not well understood, but there are evidences IL1 $\beta$  and TNF $\alpha$  promote normal sleep physiology; and mainly enhance NREM phase of sleep under normal physiological conditions, depending upon the specific cytokine, dose and timing of administration (Kapsimalis et al., 2005). They were found to act directly on the neurons of hypothalamic preoptic nucleus and basal forebrain, with IL1 $\beta$  specifically increasing discharge rates of sleep active neurons (Alam et al., 2004). Neuromodulators like 5-HT have actions like exciting and activating pain pathways in the periphery, whereas it also possesses descending inhibitory action over nociceptive transfer; which are often altered during chronic pain states (Millan, 2002). Talking about sleep, lesion in the raphe nucleus has been shown to cause insomnia in certain experiments (Koella, 1969). 5-HT1 receptors are known to be inhibitory and 5-HT2 excitatory in this respect. A network of all the intertwined systems has been depicted in the following figure 4.

We have tried to portray the interrelated and overlapping nature of these two areas of sleep and stress/pain briefly from the above discussion. Research into the genetics and genomics of these two conditions, with those that are going on

regarding the disrupted cortical networks will further strengthen this concept of overlap and probably detect a common origin; to help us devise clear and effective treatment pathways. A very good example of this was combining CBT for pain with CBT-I, which was found feasible and produced significant improvements in sleep, disability from pain, pain interference, depression, and fatigue (Pigeon et al., 2012; Tang et al., 2012).

**Figure 4: A visual summary of the pathways connecting chronic pain, depression, and sleep.**



## EFFECT OF STRESS ON SLEEP

(Di)stress leads to hyperarousal of physiological and psychological mechanisms of the body, however, on the contrary during sleep there happens deactivation over various brain areas (Frankenhaeuser, 1986). It was thus postulated that stress causes activation which when out of proportion leads to disturbances of sleep and its disorders. Initially, acute response to stress leads to a normal adaptive response by an organism, however, if the stress incommensurate and becomes chronic the harmful effects become evident on the body in many ways. Animal models have predicted that stressors have significant effects on sleep architecture and the circadian rhythm. Among animals as well as in human beings, stress ushers the activation HPA axis which in turn leads to deviation in sleep-wake cycle. The research using various animal models (Van Reeth & Turek, 1989; Van Reeth et al., 1991; Koehl et al., 1999) and human studies (Schmidt-Reinwald et al., 1999; Baker et al., 1999; McLellan et al., 1999) have proved that there is significant interplay of

dynamics between the circadian rhythm and stress. A number of sleep disorders can arise of a stressful environment, and the stressors can be both acute and chronic. Additionally, with ageing the HPA axis deteriorates gradually and there sets in various sleep related problems. This wearing-off of HPA axis with age mimics the chronic stressful environment. Evidence may also be drawn regarding the negative effects of stress on sleep from the research depicting sleep abnormalities secondary to significant life events like loss of loved ones, separation, financial loss, etc. (Vgontzas et al., 1998), in shift employees (Torsvall et al., 1989), in stress related disorders (Vgontzas et al., 1998), or in geriatric age group (Friedman et al., 1995).

The data from research on rats shows that chronic stress can negatively affect the sleep physiology and this is because of the sleep disrupting effect (Marinesco et al., 1999). There have been many efforts by lot of researchers to understand the underlying mechanisms behind stress leading to sleep disorders. It has been observed that stress induces decrease in latency to REM sleep onset, increase in total REM sleep and decrease in slow wave sleep (Cheeta et al., 1997). It is also evident that chronic stress impacts rats' endocrinial, behavioural and autonomic circadian rhythms (Koehl et al., 1999; Tornatzky & Miczek, 1993; Dugovic et al., 1999).

In human beings there is a strong relationship observed between the HPA axis activation and structure of sleep. During the early part of sleep the secretory activity of the HPA axis is significantly prone to inhibition with ACTH and cortisol levels being the lowest (Born & Fehm, 1998). The total amount of REM sleep has been positively correlated with the HPA axis activation (Vgontzas et al., 1997). Differential levels of ACTH have been shown to play a role in end of nocturnal sleep (Born et al., 1999). Onset of sleep has been evidently associated with the lower levels of cortisol (Weibel et al., 1995; Van Cauter et al., 1991). Additionally, administration of CRH, ACTH and cortisol which activate HPA axis have shown effects on the structure of sleep (Chapotot et al., 1998), and the ACTH causes delayed sleep onset, reduced deep sleep and fragmentation of sleep (Friess et al., 1995). The introduction of cortisol in pulses have led to enhanced deep slow wave sleep and reduced REM sleep (Chapotot et al., 1998). Similarly, when IL-1b or TNF are given exogenously, the increase the NREM sleep and the spontaneous sleep is decreased when they are inhibited (Krueger et al., 1998). The activation of HPA axis also impacts the immune system depicting its definite role in interactions between the stress and sleep.

Hence, it can be concluded that the stress leads to increased physiological and emotional activation responses to stressful environment and leads to activation of HPA axis which in turn has deleterious effects on the sleep physiology and normal sleep.

## STRESS AND CIRCADIAN RHYTHM

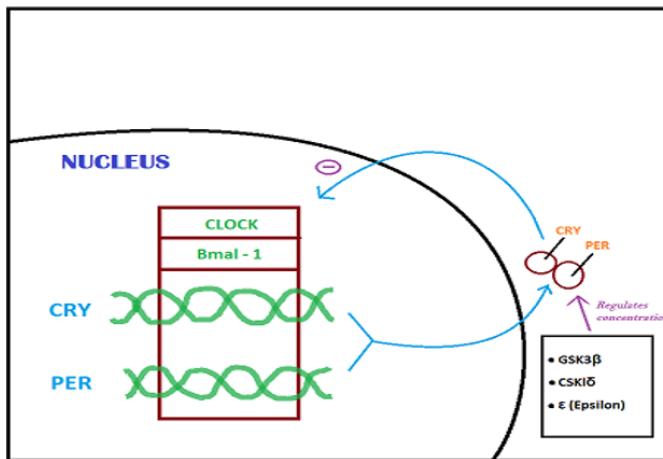
Supra-chiasmatic nucleus (SCN) which is the master circadian clock is the seat of circadian rhythm. SCN can be functionally divided into two regions- dorsomedial shell that mainly contains arginine vasopressin peptide (AVP) neurons and ventrolateral core that is rich in vasoactive intestinal peptide (VIP) neurons (Agorastos et al., 2020). These two areas have different inputs and outputs. Whereas shell receives connections from hypothalamus, core gets neurons from retino-hypothalamic tract. SCN controls a number of biological rhythms e.g., appetite, temperature, sleep and activity through its outputs to sub-paraventricular zone and dorsomedial nucleus of hypothalamus; autonomic activity through connections to pre-autonomic neurons and neuroendocrine hypothalamic areas regulating cortisol, thyroid and melatonin secretions (Agorastos et al., 2020).

SCN is considered master-clock as it regulates peripheral circadian clocks, which are present in all cells in the body and play vital role in organ functioning and metabolism. At the cellular level, circadian clock is composed of positive and negative transcriptional-translational loops that maintain the oscillation (Koch et al., 2017). Four different genes- Brain and muscle arnt-like1 (*Bmal1*), circadian locomotor output cycles kaput (*Clock*), cryptochrome 1 and 2 (*Cry*) and per 1-3 (*Per*). CLOCK-BMAL1 heterodimeric protein bind to promotor region of *Cry* and *Per* genes to enhance their transcription and translation, thus acting as positive limb of the loop. During the day, CRY-PER protein heterodimer accumulates in the cytoplasm and translocate in the nucleus to inhibit CLOCK-BMAL1 mediated transcription, functioning as negative limb of the loop (Fig 1). Concentration of CRY and PER in the cytoplasm is regulated by other proteins that degrade them viz., casein-kinase 1 delta, epsilon, adenosine monophosphate activated protein kinase and glycogen synthase kinase 3 beta (Koch et al., 2017).

As already discussed in the section of neurobiology of stress, acute and chronic stress responses are mediated through adrenaline and cortisol, respectively. Stress and circadian system interact at multiple levels (Agorastos et al., 2020). Acute stress leads to secretion of adrenaline and noradrenaline from adrenal gland. These

hormones enhance the expression of *Per1* and *Per2* genes in peripheral clocks through CAMP response element binding protein (CREB) leading to shifting of circadian rhythm (Agorastos et al., 2020; Tahara & Shibata, 2018; Tahara et al., 2017). In addition, acute stress also increase expression of *Per1* and *Per2* genes in SCN (Agorastos et al., 2020).

Figure 5: Simplified circadian clock showing feed-back mechanisms



Sub-acute to chronic stress response on circadian system is mediated through glucocorticoids (GC) that are secreted from the adrenal medulla, as already mentioned above. Studies have shown that glucocorticoids play an important role in resetting of peripheral clocks through glucocorticoids receptors (GR) (Koch et al., 2017). GC-GR complex bind to promotor regions of *Per1* and *Per2* genes to enhance their expression in peripheral cells and inducing a phase delay with reference to master clock (Agorastos et al., 2020; Tahara & Shibata, 2018). However, it is unable to rest the SCN as SCN is devoid of glucocorticoids receptors (Tahara & Shibata, 2018; Tahara et al., 2017). Thus, master rhythm remains protected during transient stress and SCN can take control after the stress is over (Agorastos et al., 2020). However, longer exposure to stress leads to habituation and stability of master clock disappears slowly (Agorastos et al., 2020; Tahara et al., 2017). Chronic stress is known to disrupt cortisol, melatonin and temperature rhythms (Agorastos et al., 2020). In addition, expression of clock genes in various areas of brain e.g., amygdala, prefrontal cortex, hippocampus and sleep-regulating areas is also altered leading to sleep disruption, cognitive changes and mood symptoms (Agorastos et al., 2020).

Interestingly, through an alternate pathway, GC also works to attenuate the uncoupling between master and peripheral clocks. This synchrony between master and peripheral clocks are effected by GC mediated enhancement of melatonin secretion (Agorastos et al., 2020). However, clinical utility of GC based synchronization is yet to be elucidated.

Timing and type of stress plays an important role in resetting of circadian clocks. In other words, it can be inferred that reactivity to different types of stress is dependent upon the circadian phase as well as types of stress (Agorastos et al., 2020). Animal studies have shown that exposure to acute and sub-acute stress in the beginning of light phase advances circadian clock while, exposure at other times of day delays it (Agorastos et al., 2020; Koch et al., 2017). Emotional stress and external physical stress shows greatest response during dark phase when GC limb of stress-response is least responsive while internal physical stress e.g., inflammation, hypoglycaemia during early phase of activity when GC limb of stress response is most active (Agorastos et al., 2020). This appears a protective mechanism to the animals as chances of experiencing external physical stress (caught by a predator) are highest during inactivity while internal physical stress is maximum during periods of activity.

In short, stress can change the circadian rhythm in body and can result in a number of adverse effects e.g., sleep disruption, metabolic syndrome and cardiovascular disorders.

## **STRESS AND POLYSOMNOGRAPHY CHANGES IN SLEEP**

Stress is known to disrupt sleep through a variety of mechanisms and it may leave the polysomnographic signatures by altering the sleep architecture. This has been examined in three different kinds of populations- first, healthy volunteers exposed to laboratory stress; second, comparison of sleep between patients with anxiety disorders and healthy controls and third, among patients having post-traumatic stress disorder (PTSD), especially war veterans.

Sleep and day to day stress have bidirectional relationship where both work in a feed forward manner. While on one hand, stress disrupts the continuity of sleep and worsens the quality, on the other hand, nights with poor sleep increase the perception of stress next day (Slavish et al., 2020). Another study reported that stress increased the sleep-onset latency, reduced amount of delta waves and

increased alpha intrusion after an acute stress in otherwise healthy individuals. However, these effects disappeared after half an hour (Ackermann et al., 2019).

A meta-analysis of sleep in patients with anxiety disorders suggested that objective measures viz., depth and continuity of sleep, total sleep time had small to moderate effect size while effect size was large for subjective sleep disturbance (Cox & Olatunji, 2020).

Subjects having PTSD have greater difficulty in falling asleep, have irregular sleep-wake schedules, report non-refreshing sleep and often use medications and alcohol to induce sleep (Baird et al., 2018). In addition, sleep after trauma is characterized by recurrent and long awakenings, reduction in proportion of deep sleep and rapid eye movement (REM) sleep and delayed onset of REM sleep (Cox et al., 2017). However, findings between stress and sleep, as mentioned above, are not consistent (Cox et al., 2017). Stress appears not to affect actigraphy and electroencephalographic parameters in otherwise healthy individuals as well as among patients with PTSD (Cox et al., 2017; Slavish et al., 2020). This difference could be ascribed to a number of factors e.g., resilience, sleep reactivity, type and severity of trauma, comorbid other medical disorders, use of addictive substances and medications, gender and age to name a few. First night effect is another important issue that should be considered in polysomnographic studies. A recent study showed that effect size for polysomnographic parameters e.g., sleep onset latency, total sleep time, wake after sleep onset, arousal index, proportions of sleep stages increased on second night compared to first night when comparison was made between patients with and without PTSD (Wang et al., 2020). Alternatively, it is possible that PTSD does not affect the sleep macro-architecture but influence the micro-architecture. A recent study has shown that patients with PTSD show reduced delta-power over central and parietal region during NREM sleep as well as increased gamma frequency in antero-frontal regions during NREM as well as REM sleep (Wang et al., 2020). These findings explain that patients with PTSD remain in a state of hyperarousal and why they often complain of non-refreshing sleep (Wang et al., 2020).

Thus, stress affects various parameters of sleep, however, results regarding objective parameters are inconsistent. Study of sleep micro-architecture explain most of the clinical symptoms reported by patients experiencing stress.

## EFFECT OF MANAGEMENT OF STRESS ON SLEEP AND VICE VERSA

Stress can be managed through pharmacological as well as non-pharmacological measures. Most commonly pharmacotherapeutic approach to manage stress are anxiolytics, particularly benzodiazepines. However, benzodiazepines allay anxiety through GABA agonistic action that also induce sleep. Hence, benzodiazepines are not the ideal candidates to understand the relationship between these two factors. However, non-pharmacological methods e.g., slow breathing and listening music have been found to reduce sympathetic activity and increase deep sleep, yet effect were not robust (Kuula et al., 2020). Similarly, Jacobson's progressive muscular relaxation for three days has been found to improve subjective sleep quality and reduce anxiety among burn patients (Harorani et al., 2020). Another study showed that practice of Benson's relaxation technique for four weeks, 20 minutes each day improved sleep quality among elderly (Habibollahpour et al., 2019). Preliminary evidence shows that relationship between sleep and stress is bidirectional. Improvement in sleep has been found to reduce perception of stress among healthy volunteers (Steffen et al., 2015).

## MANAGEMENT OF SLEEP DISORDERS ARISING OUT OF STRESS

Sleep disorders can be managed through a number of non-pharmacological as well as pharmacological methods. Whereas non-pharmacological methods primary work to reduce perception and impact of stress, pharmacological measures primarily work through stabilizing the neurocircuitry changes that arise out of stress. Thus, the literature suggests that ***non-pharmacological manipulations*** to reduce stress as well sleep can work in feed forward manner. Non-pharmacological measures include various strategies to reduce stress that include:

### I. Time management

One of the major source of stress is poor time management. Conceptualized by McCay in 1959, and developed subsequently by others, the primary elements of time management skills include giving insight into time-consuming activities, altering time expenditure routine, and enhancing work efficiency by teaching people how to make a daily planning, how to prioritise tasks, and how to handle unexpected tasks within the time schedule. Reviews have found that time management behaviours relate positively to perceived control of time, job satisfaction, and health, and negatively to stress (Claessens et al., 2007).

## II. Relaxation exercises

- a) Jacobson progressive muscle relaxation:

Described by Edmund Jacobson in 1930, it is based upon his premise that mental calmness is a natural consequence of physical relaxation. It is achieved by pairing inhalation and exhalation with contraction and relaxation of groups of muscles, in order, and trying to focus on the changes one feels during the release of muscle tension; often accompanied with relaxing imagery.

- b) Yoga techniques:

*Pranayam* has been defined by Macdonell as the suspension of breath. It not only consists of synchronising the breath with movements between *asanas*, but is also a distinct breathing exercise on its own, usually practised after *asanas*.

*Shavasana* also known as corpse pose, often done at the end of most of the yoga practices, focuses on feeling the relaxation while breathing deep and lying in a prone position. *Yoga Nidra* is a state of complete relaxation, where all the five senses are somewhat withdrawn, barring the auditory sensation, which follows instructions. The modern version given by Satyananda Saraswati, consisted of stages: internalisation, sankalpa, rotation of consciousness, breath awareness, manifestation of opposites, creative visualization, sankalpa and externalisation.

## III. Cognitive behavior therapy for insomnia

Provided by a trained clinician in a four – eight session period, it initially aims at identifying the underlying causes of insomnia and applying the components of CBT-I accordingly. It usually consists of psychoeducation/sleep hygiene, sleep restriction, relaxation training, stimulus control, cognitive therapy and paradoxical intention. Most of the 15 meta-analyses published have concluded good effects of CBT-I in insomnia patients. Based on two meta-analyses which directly compared CBT-I with pharmacotherapy, it has been concluded that CBT-I and hypnotics have comparable efficacy in the short term, and that the former is superior in the long term (Riemann et al., 2017).

## IV. Pharmacological methods

Although many medications have shown to be having sedating and hypnotic properties, it is the Benzodiazepines and BZD Receptor Agonists, which have shown the maximum efficacy and are most commonly used as well in the short term treatment of insomnia. Besides, other psychiatric diagnoses should be managed

by their respective class of medications (i.e. Antidepressants, Antianxiety, etc.) to reduce the stress accompanying them.

## CONCLUSIONS

Evidences of overlap between the neural circuits underlying the pathways of stress and sleep, epidemiological and laboratory studies, including PSG studies, highlighting the consequences of stress on the sleep physiology leads the reasonable mind to delve deeper into the interconnections of these two vital components of life. The reciprocal benefits observed in one of these two, when the other is treated, leaves none surprised. Ongoing research tends to promise of definitive treatment modules which will combine such benefits and help the mankind to balance this interdependence of stress and sleep equally well.

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## **STRESS AND SEXUAL DISORDERS**

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### **OUTLINE**

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## **INTRODUCTION**

In the initial chapters of the book, stress has been defined and understood. It was Selye, in 1956, who first used the term “stress” to indicate an event that disrupted “homeostasis”. Cannon, in 1929, gave the term homeostasis to an inclusive idea given by Claude Bernard, that maintenance of life is dependent on a stable internal environment, in relation to the dynamic external environment (Bernard, 1865). Stress is defined as “a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her wellbeing” (Lazarus & Folkman, 1984). Stress can be classified based on the duration as acute, sub-acute or chronic, and based on the intensity as mild, moderate or severe. The stress encountered by a person can be various combinations of duration and intensity. The stressful event and response i.e. intensity is a subjective experience and cannot always be measured objectively. However, the effect of stress on individuals can be varying and it is of utmost importance to identify, evaluate and treat it to minimize these effects on the body and mind. The word stress, in this chapter will refer to psychological or social stress.

In the field of psychiatry, sexuality and sexual disorders both in clinical and research areas have increasingly been emphasized in the last few decades. Sexual functioning is encompassed by complex biological, social and psychological factors (Avasthi et al., 2017). The prevalence of sexual disorders is estimated as high as 43% in females, and 31% in males. The sexual disorders are under-diagnosed, under-recognized in the clinical settings which is attributable to poor comfort levels regarding discussing sexual functioning in both the patient and clinician. Hence it becomes important for the clinician to initiate the discussion, make the patient comfortable, establish confidentiality and understand the patient through his lens.

It is also important to understand that sexuality goes beyond the concept of sexual functions or dysfunctions alone. Cultural sexual beliefs (myths), like masturbation leads to loss of potency is a commonly seen in men of the Indian subcontinent who consult for performance anxiety. Several such beliefs exist across the globe. There is a need to be sensitive to the background of the patient, along with having adequate training and expertise in understanding and treating sexual disorders. Sexual disorders can be broadly categorized as disorders of sexual identity, paraphilic, disorders based on the sexual cycle. In this chapter we will look at the sexual disorders based on sexual cycle. The other sexual disorders are important, but beyond the scope of the chapter. In this chapter we will specifically look at stress and its effects on sexual disorders. Stress is equivalent to psychosocial stress, unless otherwise mentioned. As we try and understand we see that the effect of stress on sexual functioning could be bidirectional, i.e., increased stress could cause sexual dysfunction and vice versa. There are also reports of stress increasing sexual activity, as a stress buster. The details of these will be discussed later in the chapter.

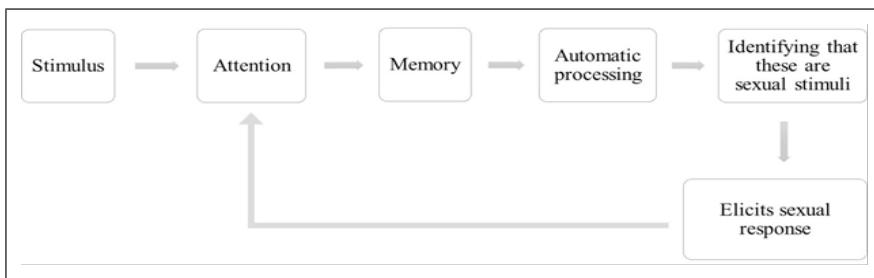
## THE SEXUAL CYCLE MODELS

The extensive experiments and studies by Masters and Johnson described the sexual response cycle called excitement, plateau, orgasm, resolution (EPOR) model. Kaplan and Lief then identified EPOR being a predominantly genital focused model, and qualified desire to be an important aspect, and described the desire, excitation, orgasm, resolution (DEOR) model. Then came the circular model of Whipple and McGreer incorporating four stages of Reed's (1998) Erotic stimulus pathway, namely, seduction (desire, attraction), sensations (excitation and plateau), surrender (orgasm) and reflection (resolution). Sexual Tipping Point (STP) model by Perelman based on the fact that mental and physical (MAP) factors influence inhibition or excitement

in sexual activity. There are various other models like Basson circular model, 4 Es model, the cusp catastrophe model, dual control model, the sexual man model and others. The physiological human sexual response cycle described by Masters and Johnson is the most commonly used model in assessment and psychotherapy. The book “Human Sexual response” by Masters and Johnson (Masters & Johnson, 1966) has given a diagrammatic representation of male and female sexual response cycle and would be useful to refer to it to understand the concepts.

The Information Processing Model (Janssen et al., 2000) demonstrates the physiological, psychological (cognitive and affective) and behavioral components. The same is represented in the flowchart below (See Figure 1).

**Figure 1: Information Processing Model**



### **Neurobiological factors associated with sexual response (B- head)**

The sexual response cycle is not as simple as it seems. The stages observed have a neuro-endocrine basis to each of them. In the table (See Table 1) below we have enumerated the various neuro-endocrine systems which enhance or inhibit the sexual response phases.

**Table 1: Neuroendocrine basis of sexual response**

Stage	Enhancers	Inhibitors
Desire	Testosterone, Dopamine, Inhibition of 5HT-2C and 5HT-2A serotonin receptors	Prolactin, Serotonin
Erection	Parasympathetic nervous (Cholinergic) system, Dopamine	Sympathetic nervous system
Ejaculation	Sympathetic nervous system, Dopamine	Serotonin

## CLASSIFICATION OF SEXUAL DISORDERS

The most commonly used classificatory systems currently are the ICD-10 and DSM-5. The classificatory systems are fairly different from each other, especially with respect to the terms used to describe the sexual disorders, for example, lack or loss of sexual drive in ICD-10 is hypoactive sexual disorder in DSM-V. The DSM-5 and ICD-10 diagnoses of sexual disorders in relation with sexual response cycle is provided below (See Table 2).

**Table 2: Sexual response cycle and sexual disorders**

Sexual response cycle	DSM-5	ICD-10
Excitement	Erectile disorder Female sexual interest/arousal disorder Male hypoactive sexual desire disorder	Lack or loss of sexual desire Sexual aversion and lack of sexual enjoyment Failure of genital response Excessive sexual drive
Orgasm	Delayed ejaculation Premature (early) ejaculation Female orgasmic disorder	Orgasmic dysfunction Premature ejaculation
Others	Genito-pelvic pain/penetration disorder	Nonorganic vaginismus Nonorganic dyspareunia

## BIO-PSYCHO-SOCIAL ASPECTS OF SEXUAL FUNCTIONING

The sexual functioning can be attributed to biological and psychosocial factors. When the biological aspects of sexual functioning are altered primarily, it is known as organic sexual dysfunction. When the psychosocial aspects are identified as the primary cause, they are called sexual disorder without organic causes

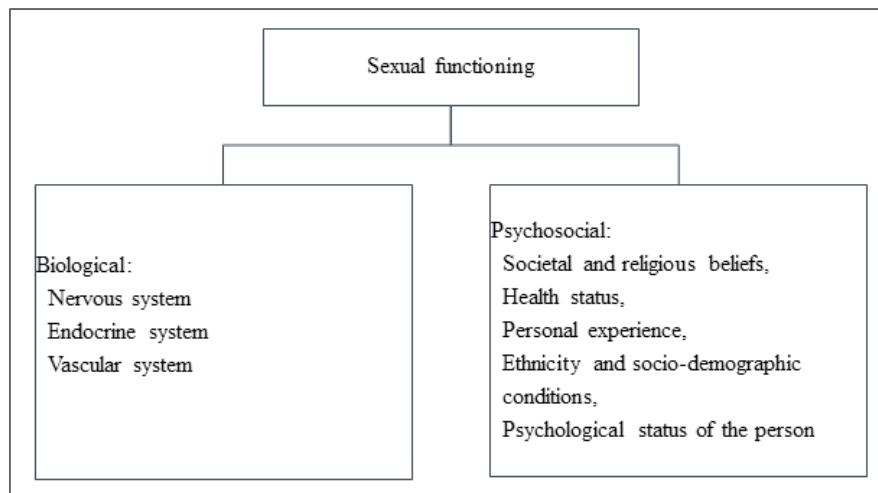
In biological aspects, hormonal disorders like diabetes mellitus, thyroid disorders, decreased estrogen and decreased testosterone levels have variable effects on sexual desire and arousal phase respectively. Similarly, neurological and vascular disorders, surgeries, chronic illnesses also have bearing on the general physical health, also on sexual functioning. The mechanisms by which they result in sexual dysfunction is not discussed in detail as it is beyond the scope of this chapter.

Psychologically, sexual behavior is also a type of learning, any negative events in the past, like severe pain, sexual abuse, sexual assault would negatively influence

sexual desire and similarly positive sexual outcomes and pleasure increase sexual desire (Koneru et al., 2019).

It is important for us to understand various aspects of sexual functioning and factors that influence it (See Figure 2) to be able to understand the person and be able to provide holistic care. The interventions for sexual dysfunction would be dependent on its cause. Hence, understanding the causes and how it affects the sexual functioning is of utmost importance.

**Figure 2: Factors influencing sexual functioning**



The assessment of sexual functioning, initial focus should be to establish sexual disorder and rule out myths associated to sexual functioning. Once sexual disorder is established, it is important to see if the sexual functioning is predominantly organic or psychogenic in nature. Older age, gradual onset, global decline in sexual activity, no fluctuation with situation or change in partner, consistent and progressive deterioration in functioning, intact desire for sexual activity usually indicate towards organic causes. The sexual disorders which on evaluation are usually inconsistent, intermittent, sexual desire is affected more often than others, age of onset is younger age of onset suggest psychogenic origin. It is important to know that in most cases, there is an overlap or mix of both psychogenic and organic components. One should evaluate both – psychogenic and organic in detail before making a diagnosis or initiating treatment. The mental health professionals' prejudices and rigidities should not interfere with the evaluation. A non-judgmental

and non-prejudiced attitude is an important to make the patient feel comfortable in discussing sexual problems. The next phase of assessments in psychogenic sexual disorders is to look at the three key components of psychosocial functioning in relation to sexual disorders, initially described by Hawton and Caplan namely predisposing, precipitating and maintaining factors of sexual disorders (See Table 3) (Althof & Needle, 2013; Avasthi et al., 2017). This helps us understand the dynamic interplay between the body and the mind.

**Table 3: Key components of psychosocial functioning and sexual disorders**

Predisposing factors	Precipitating factors	Maintaining factors
Early life events which put a person at risk for developing sexual dysfunction or to be resilient	Factors that can trigger the onset of sexual disorders	Factors that may prolong the problem
<ul style="list-style-type: none"> <li>• Restrictive upbringing</li> <li>• Disturbed family relationships</li> <li>• Traumatic early sexual experience</li> <li>• Inadequate sexual information</li> <li>• Insecurity in the psychosexual role</li> <li>• Distraction</li> </ul>	<ul style="list-style-type: none"> <li>• Unreasonable expectations</li> <li>• Random failure</li> <li>• Discord in the relationship</li> <li>• Dysfunction in the partner</li> <li>• Infidelity</li> <li>• Reaction to organic disease</li> <li>• Pregnancy/Childbirth</li> <li>• Poor emotional intimacy</li> <li>• Expectation of negative outcome</li> <li>• Depression or anxiety</li> </ul>	<ul style="list-style-type: none"> <li>• Performance anxiety</li> <li>• Guilt</li> <li>• Poor communication</li> <li>• Loss of attraction between partners</li> <li>• Impaired selfimage</li> <li>• Restricted foreplay</li> <li>• Poor emotional intimacy</li> <li>• Depression or anxiety</li> <li>• Expectation of negative outcome</li> <li>• Fear of intimacy</li> <li>• Sexual myths and misconceptions</li> <li>• Poor communication</li> </ul>

## STRESS AND SEX

Is sex a stress buster or a stress inducer? It is so often that we hear people telling they resort to sexual activity to feel better, release frustration, which is also seen as sexual healing (Ein-Dor & Hirschberger, 2012). There are not many studies which specifically look at how stress affects sexual functioning. In a study by Bancroft and colleagues, they have studied effects of stress on male sexual functioning and noted 16.6% of men had decreased erectile response, 10.6% men had increased erectile response, 28.3% had increased sexual interest and 20.6% had decreased

sexual interest. In a study by Bodenman, who looked at stress and its relation to sexual activity found chronic daily stress decreased frequency of sexual activity, reduced desire, caused sexual aversion, vaginismus and pre-mature ejaculation (Bodenmann et al., 2006). Bodenman in one of his papers has described increased daily hassles to have increased sexual desire in men and women, with the moderator being relationship satisfaction. However, these findings have not been established, or replicated in large samples. They give perspectives and understanding into the complex human behaviors in relation to sexuality and understanding sexual behaviors. In sexual activities there are certain terms like sexual phobia, phobic response, anticipatory anxiety which are used in relation to understand and approach sexual behaviors. Sexual phobia is also called sexaphobia, is the total aversion and avoidance to any experience, feeling, thoughts or sensations related to sexual activities. Phobic sexual response is usually limited to specific acts of sexual activity like oral sex, homosexual activity, etc. All patients with any phobic anxiety related to sex/sexual functioning develop anticipatory anxiety and avoid sexual situations as a coping strategy. It is important to understand the various presentations to be able to understand sexuality and sexual behaviours to be able to provide appropriate pharmacological and psychological intervention.

### **Mechanisms by which stress affects sexual functioning**

The relationship between stress and sexual dysfunction is like the chicken or egg situation. Whether the effects are causal or consequential is difficult to establish at times. However, one should note that stress can precipitate and maintain sexual dysfunction. Sexual dysfunction leads to low self-esteem, poor body image, preoccupation with performance, troubled inter-personal relationships and increase stress (Mollaioli et al., 2020). Hence the relationship between stress and sexual disorders can lead to a vicious cycle of negativity, increase experienced stress and its effects on a long duration. Below we shall look at physiological and psychological ways by which stress leads to sexual disorders.

Acute stress mediates its negative effects on sexual functioning by increased production of catecholamines. Moderate levels of nor-epinephrine are found to be good for sexual functioning, but high levels, associated with generalized fear response is sexually inhibitory (Barata, 2017).

Chronic stress promotes the release of cortisol releasing hormone (CRH) from anterior pituitary acts on adrenal cortex and increases levels of cortisol. Cortisol

decreases gonadal steroids and decreases adrenal androgens. The lowered level of gonadal steroids and adrenal androgens have negative effects on desire, libido, arousal, and negative impact on number and morphology of sperms. Chronic stress can also weaken one's immune system leading to infections of genito-urinary tract leading to sexual dysfunction.

Through the psychological model of understanding, stress prevents oneself from focusing on the sexual stimuli through distraction where the person is focused on non-sexual stimuli making them have low satisfaction in sexual activity. Stress and anxiety may dismiss sexual stimuli or misinterpret a non-sexual stimulus to have a sexual meaning i.e., misattribution style of thinking. It is seen though non-conclusively that stress and sexual functioning have an inverted-U shaped relationship i.e., very low and very high levels of stress impair sexual functioning and moderate levels of stress (also optimal stress) improve sexual functioning.

### **Various stressors and their association to sexual disorders**

#### *Burn out and occupational stress*

Burnout or "job burn out" is defined as a state of emotional and psychological exhaustion. Similarly, hectic working schedules also put people at risk for facing occupational stress and job stress. In men, personal burnout was seen to have high association with Erectile Disorder (ED) and reduced satisfaction from sexual activity. The other factors that were significantly associated with the same are alcohol use and hypertension. Alcohol use had relation to ED, reduced orgasms, poor satisfaction. Hypertension caused ED and reduced satisfaction. In women, burn out was associated with reduced orgasms, poor lubrication.

Unemployment is seen to be associated with erectile dysfunction in men. It is noted that rate of decrease in erection with age is higher in unemployed men (Morokoff & Gilliland, 1993).

#### *Lifestyle based stress-modifiable factors*

**Decreased physical activity** will reduce endothelial nitric oxide and increase oxidative stress (molecular level) which results in poor vasodilation and erectile dysfunction.

**Stress induced weight gain** reduces insulin sensitivity, decreases plasma testosterone and increases estrogen secondary to conversion of Dihydroepiandrosterone (DHEA) in peripheral adipose tissue and this can cause erectile dysfunction.

Stress either causing or increasing **nicotine use** (smoking/chewable) causes erectile dysfunction through poor vascularization, reduced nitric oxide.

**Alcohol use**, at lower quantity of consumption, causes disinhibition and makes people promiscuous or at high risk for unprotected sexual intercourse. However, alcohol consumption at high quantities of regular use in dependence pattern in men has neuro-vasculo-degenerative and hormone toxicity, causes erectile dysfunction in men and decreased vaginal lubrication, decreased desire and inability to attain orgasm in women, unsatisfactory sexual performance in both men and women.

### **Interpersonal relationship with spouse**

It has been noted that happy couples have a higher frequency of sexual intercourse as compared to unhappy couples, and marital satisfaction is positively correlated with sexual satisfaction (Morokoff & Gilliland, 1993). However, in most relationships, sexual activity is not a chore, it demonstrates emotion, love, intimacy and comfort level between the couple. If there is poor emotional bonding, marital issues, ongoing divorce, these factors tend to interfere with sexual functioning. Hence, we can understand that sexual and relationship satisfaction go hand in hand. Intervention in couple settings work well when the emotional and sexual component are handled simultaneously (Althof & Needle, 2013).

### **Chronic stress**

Chronic stressors and daily hassles are deleterious to physical and mental health of a person, including sexual activity. Hamilton and colleagues used Hassles scale to assess daily hassles and then evaluated its relation to sexual functioning. Depressive symptoms were seen to be major mediators affecting sexual functioning. Daily financial related stressors had significant effect on sexual functioning in women, not in men. Ter Kuile et al described chronic stress in women resulted in reduced genital arousal, but no change in subjective arousal (Ter Kuile et al., 2007).

### **Psychiatric disorders and sexual dysfunction**

The realm of the individual psychiatric disorders and how they lead to impairment in sexual functioning might be beyond the realm of this chapter. However, we should understand that stress can lead to psychiatric disorders of both the neurotic and psychotic spectrum. Psychiatric disorders, owing to the neurobiological

changes, cognitive distortions/biases can lead to sexual dysfunctions. There is a high correlation between panic disorder and sexual aversion (Bodinger et al., 2002). In social phobia, men have more performance related disorders (Morokoff & Gilliland, 1993; Bodinger et al., 2002) and women have more pervasive disorders (Bodinger et al., 2002). The symptoms of depression make it difficult to have intimate relationships (Baldwin, 2001). Low sexual desire is the most common sexual disorder associated with depression, some studies have also reported increased sexual desire, premature ejaculation, and others. People with early childhood trauma, developing chronic illness, high cardiovascular risk, cancers, diabetes and other endocrine disorders are at a higher risk for depression, and the complex interaction of the Hypothalamo-Pituitary-Adrenal (HPA), Hypothalamo-Pituitary-Gonadal (HPG) axis may also make them at a higher risk to develop/maintain sexual dysfunction. One should also remember that antidepressants cause erectile dysfunction as a side effect, however also cause delayed ejaculation and are commonly used in treatment of premature ejaculation. Antipsychotics cause increase in prolactin levels causing ED. The various disorders, like post-traumatic stress disorder, schizophrenia, delirium and all the known psychiatric disorders would have varied effects on sexual functioning either by virtue of the illness itself, or as an adverse effect of the medications given.

## **TREATMENT OF SEXUAL DYSFUNCTION DUE TO STRESS**

When a person consults a physician for sexual dysfunction it is advisable to rule in psycho-social factors, stress being a common culprit. Many may have not recognized chronic stress in their life and would have not associated chronic stress to sexual dysfunction. They may, in fact have thought the opposite, that lack of sex causing stress. Unless the underlying stress is taken care of, the sexual dysfunction may be difficult to be treated. Many may not respond to only psychoeducation and would require psychotherapy to alleviate stress. Physical exercise, breathing exercises, yoga, and meditation also play a role in reduction of stress, thereby improving sexual dysfunction. Stress leading to sexual dysfunction in one partner may lead to thoughts of rejection in another partner, and couple therapy may help in this regard.

## **CONCLUSIONS**

Sexual functioning is a complex phenomenon encompassing bio-psycho-social factors. Stress has a bidirectional relationship with stress. Stress can affect all the

aspects of sexual response cycle, both biologically by neuro-endocrine mechanisms and psychologically by negative thoughts of anxiety, guilt, negative self-image, etc. Treating underlying stress is important in the treatment of sexual dysfunctions.

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## **Stress & Eating Disorders**

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| 1. INTRODUCTION | 2. BIOLOGY OF FEEDING BEHAVIOUR &<br>EATING DISORDERS |
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## **INTRODUCTION**

Eating disorders are a group of disorders characterised by aberrant patterns of food intake or eating. They involve abnormalities in several aspects of feeding behaviour such as deliberate restriction of food intake due to body shape and weight gain concerns (anorexia nervosa). Some may also involve episodic uncontrolled overeating (binge) followed by compensatory measures to reduce or maintain weight (purgung). These are predominantly seen in disorders like bulimia nervosa (binge and purge) or binge eating disorder and night eating disorder (binge eating). Some of these eating disorders are associated with medical complications and increased mortality.

Stress has an etiological role in the onset of eating disorders and can play a role in maintaining or relapse of these disorders as well. The role of stress in the onset and maintenance of eating disorders can be easily understood when we look at the two types of feeding: Homeostatic feeding and non-homeostatic feeding. Homeostatic feeding is also known as metabolic drive or hunger and is driven by the metabolic milieu of the body. It is determined by neural and biochemical activity in the hypothalamus and nearby areas of the brain. The non-homeostatic

feeding is driven by the emotional state also known as hedonic feeding where stress, anxiety, depression and other negative emotional states play a major role.

In this chapter we will briefly review the neurobiological underpinnings of feeding behaviour and eating disorders and how stress and emotions can modulate them to lead to the onset, maintenance or relapse in eating disorders.

## BIOLOGY OF FEEDING BEHAVIOUR & EATING DISORDERS

### **Homeostatic feeding**

The homeostatic feeding (hunger driven) is linked to the metabolic state of the body. Increased glucose, insulin or leptin levels lead to inhibition of hunger. On the other hand, high ghrelin levels can stimulate hunger through the activation of Agouti-Gene Related Peptide (AGRP) release from the Arcuate Nucleus. This seems to be the final common pathway for the homeostatic feeding drive. In animal models, the ablation of the AGRP neurons in the arcuate nucleus leads to a loss of the drive to feed. The suppression of ParaBrachial Nucleus (PBN) by the use of benzodiazepine Bretazenil in turn rescued the appetite. This rescue is possibly due to the negation of excitatory inputs from Nucleus Tractus Solitarius (NTS). The NTS relays excitatory inputs to the PBN when the animal is fed with tasty or palatable food. There are in turn serotonergic innervation to the NTS from the raphe nuclei (magnus and obscurus; not dorsal raphe), the ablation of which could also lead to rescue feeding in AGRP deficient mice. There is an in-depth review by Sternson, (2013) that gives the details of this pathway.

### *Non-homeostatic feeding*

The other major drive for feeding is non-homeostatic or hedonic feeding which is important for understanding the link between stress and eating disorders. This pathway particularly involves the ingestion of palatable food, high sugar or carbohydrate or high fat content food, which are perceived as tasty and this pathway is particularly activated when such foods are orally ingested rather than by any other route (or direct infusion through a nasogastric tube) which highlights the ‘hedonic’ nature of this feeding. Table 1 summarises some of the major aspects of homeostatic and hedonic feeding.

### *Role of stress in feeding and eating disorders*

In this regard the major hormones involved are Corticotrophin Releasing Hormone (CRH) and glucocorticoids such as cortisol and corticosterone. These

hormones belonging to the Hypothalamic-Pituitary-Adrenal (HPA) axis system or the stress-response system have some direct effects on appetite and feeding behaviour in animal models. They have also shown to be altered in patients with eating disorders. The study of the effect of stress on eating disorders needs to consider a few important aspects – (1) the etiological role of stress versus secondary alteration of stress hormones in patients who restrict calories; (2) the effect of acute versus chronic stress on feeding and eating behaviours.

### **Stress relieving effects of food intake**

*Acute stress:* When an animal is faced with acute stress, time limited access to a small amount of sugar solution helped the rats overcome the effects of stress. This is the Limited Sucrose Ingestion (LSI) paradigm in rat model. This is also called as the “snacking” model (Ulrich-Lai et al., 2017). Studies in human beings have also shown that a substantial proportion of human beings tend to eat more total calories when faced with stress (Oliver & Wardlee, 1999). High carbohydrate food in particular can help in reducing stress, improve mood and lowers cortisol levels. “Comfort” foods have been defined as palatable, tasty and often high calorie food with a potential to relieve stress. These foods cause stress relief by virtue of the rewarding effects of tasty food. The stress relief effects are noted on oral ingestion, but not on orogastric gavage of the sugar solution. The neurobiological basis for this rewarding effect of palatable food and stress relief is said to be changes in the Basolateral Amygdala (BLA) which has demonstrated increased neuronal activity as well as increased cFos expression. There is also increased expression of genes involved in synaptic plasticity indicating a long-term potentiation model. These have been reviewed in detail in (Ulrich-Lai et al., 2017).

*Chronic stress:* This anxiety lowering, stress relieving effect of food is of short-term benefit and with time the HPA axis activation remains high and there is sustained ingestion of high calorie palatable food. Thus, increased consumption of “comfort foods” by individuals over time leads to development of weight gain and obesity (Fulton, 2010). Neurobiologically, sustained consumption of high-calorie palatable food leads to changes in the Nucleus Accumbens (NA) along with increased phospho-Cyclic-AMP Related Binding Protein (pCREB) and Brain Derived Neurotrophic Factor (BDNF) expression in this region. These changes are responsible for depression-like behaviour in animal models (Russo & Nestler, 2013). These changes also overlap those seen in addictive disorders. This is called as the reward-deficit paradigm with a reduced dopaminergic transmission and

increase in NA synaptic density seen in people with obesity (Wang, 2001). These changes in turn sustain prolonged consumption of high-calorie diet in the face of acute or chronic stress. However, as time progresses and there is weight gain, the HPA axis activation remains high and the stress lowering effects of High Fat Diet (HFD) is gradually lost (Sharma & Fulton, 2013).

With repeated cycles of stress-induced eating, there is development of Diet-Induced Obesity (DIO) over time. Diet-Induced Obesity (DIO) is a risk factor for diabetes mellitus as well as depression. In these individuals, high amount of saturated fats in the diet leads to central or abdominal obesity (Rosqvist et al., 2014). Moreover, it has been shown that high saturated fat diet also leads to a relative deficiency of unsaturated fats and essential fatty acids such as omega-3 (w-3) fatty acids, which can increase the risk of depression (Oddy et al., 2011). These behavioural consequences were associated with increased basal HPA activity and greater stress. Thus, increased food intake secondary to repeated bouts of acute stress can lead to obesity, which in turn can lead to anxiety, depression and chronic activation of stress response, further driving consumption of high calorie food in a vicious cycle. Figure 1 depicts the stress induced feeding cycle and how it leads to obesity and further stress over period of time.

Finally, the role of social stress in modulation of food intake and “comfort” eating has been demonstrated in male rodents and female monkeys. It has been shown that when submissive animals are placed in the presence of dominant ones, the stress leads to increased consumption of highly palatable food when a choice of food is available (Michopoulos et al., 2012). The dominant animals do not tend to consume more of the highly palatable food even when available. This phenomenon is also believed to be a result of the aforementioned cycle of stress induced feeding and the high basal levels of activation of HPA axis in submissive animals which have consumed HFD. This points to the role of exposure to stress as well as availability of HFD (which usually is the case in humans) in the genesis of eating disorders.

The above reviewed studies point out to the potential mechanisms by which stress can lead to binge eating in eating disorders such as bulimia nervosa and binge eating disorder. The next section will look at the mechanism of stress induced feeding restriction such as that seen in anorexia nervosa.

## Food restriction in the wake of stress

Rat models have shown that when aversive stimulus (foot-shock) are presented, it leads to inhibition of food consumption in hungry rats. Such a learning is shown to occur by classical conditioning experimental paradigms. In these experimental paradigms, the inhibition of food intake was triggered even when the animal was placed in the same conditioning context (same environment) as during the delivery of foot-shocks to inhibit feeding. It was noted that the freezing behaviour of rats (immobility except for breathing movements) and inhibition of feeding related behaviour (approach to food, ingestion and licking movements) are both distinct. The central amygdala (CeA) was responsible for food restriction in the wake of aversive stimuli (Petrovich et al., 2009). This role of the central amygdala is in contrast to the role of Basolateral Amygdala (BLA) elucidated in the previous section (see Stress relieving effects of food intake).

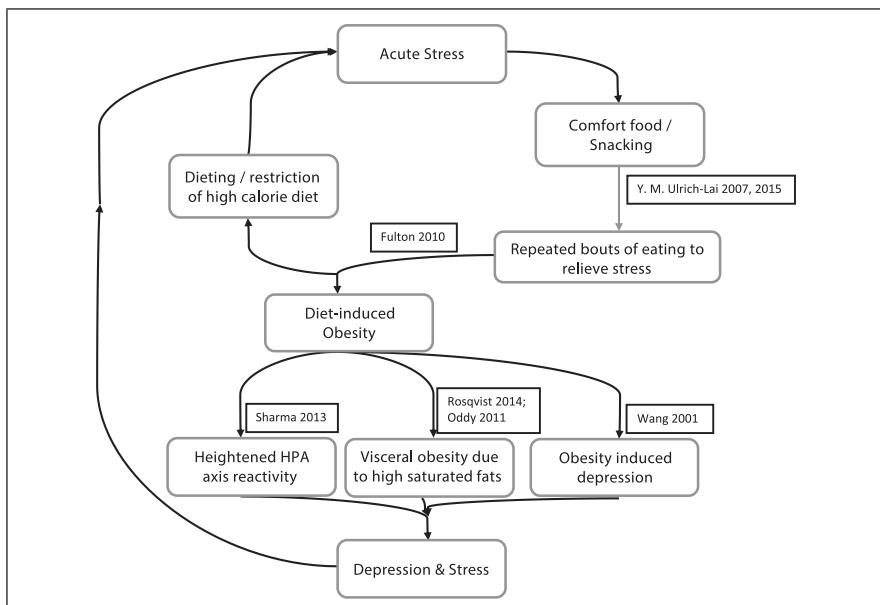
Table 1: Neurobiological aspects of Eating and Feeding Behaviour

State	Increase	Decrease	Brain regions involved	Brain changes described
Homeostatic feeding				
Satiety	Glucose Insulin Leptin	-	Parabrachial Nucleus – which is stimulated by excitatory inputs from Nucleus Tractus Solitarius (when tasty food is consumed)	-
Hunger	Ghrelin	Glucose Insulin Leptin	Arcuate nucleus	Agouti-Gene Related Peptide (AGRP) release
Hedonic feeding				
State	Model	Effects on stress	Brain regions involved	Brain changes described
Acute stress	Limited Sucrose Intake (snacking)	Reduces stress	Basolateral Amygdala	Increased cFos expression in BLA
Repeated episodes of stress induced eating	High Palatable Food, High fat content	Reduces stress (less effective over time)	Nucleus accumbens	Increased pCREB and BDNF expression leads to reward deficit state (anhedonia / depression) less responsive HPA axis

State	Increase	Decrease	Brain regions involved	Brain changes described
Chronic stress	High saturated fat content	HPA axis is chronically activated		
Stress induced restriction of feeding	Rat foot-shock	Freezing behaviour and Restriction of feeding	Central Amygdala	This restriction of feeding undergoes extinction in males, but not as easily in females. Estrogen has appetite suppressant effects and may play a role in anorexia nervosa

There was also differential response among males and females to food restriction. In male rodents, the food restriction response showed extinction from the second trial. However, female rodents took longer to show extinction of food restriction in response to aversive stimuli (Petrovich & Lougee, 2011). This sex-difference noted is significant because we find that anorexia nervosa is far more common in adolescent girls than in boys. The possible reason

Figure 1: Schematic diagram showing the role of stress in binge eating



for the sex-differences is the milieu of ovarian hormones - estrogen and progesterone. Increase in estrogen levels post-puberty places adolescent girls at greater risk of anorexia due to the anorexigenic effects of estrogen. This anorexigenic effect of high estrogen is prominent in the pre-ovulatory phase when progesterone levels are low. However, in the postovulatory phase, as the progesterone levels rise, it opposes the anorexigenic effects of estrogen to cause greater risk of emotional eating in vulnerable adolescents (Culbert et al., 2016). Hence the ovarian hormone milieu may have an effect on both – food restriction as well as binge eating or emotional eating.

### **The role of epigenetic mechanisms:**

Epigenetic mechanisms are the influences of environmental factors on gene expression (or silencing) and they help us in the understanding of how environmental adversities may lead to uncovering of genetic vulnerabilities to certain disorders. The most common mechanism of epigenetic influences is the methylation of gene promoter regions containing Cytosine-Guanine (CpG). This methylation leads to silencing of the particular genes which may have a protective role in certain disorders.

With respect to Eating Disorders (ED), there is some evidence for the role of stress at three major time points – intra-uterine stress, early-life stress (infancy and childhood) and later-life stress (adolescents) which may have a potential role in the etiopathogenesis of ED. In this regard, it has been found that offspring of Canadian mothers who were exposed to harsh winter of 1998 Quebec Ice Storm were more susceptible to development of eating disorders (St-Hilaire 2015). This can be understood as a mechanism by which the exposure to calorie deficiency in foetal life leads to epigenetic changes which enables accumulation of energy stores or calories in times of stress and relative food excess. Studies have also shown that exposure to early-childhood stress and child abuse is a risk factor for emotional instability as well as eating disorders like bulimia nervosa, or binge eating (Steiger et al., 2013). This is mediated commonly through the heightening of HPA axis responsiveness (Liu et al., 1997). Finally, it has been noted that all EDs, especially the restrictive forms typically characterised by Anorexia Nervosa (AN), are associated with DNA methylation changes across a wide range of genes which can explain the onset of maintenance of ED (Strober et al., 2014). Further detailed research in this area is required to elucidate these pathways in detail.

### **An integrated view of the role of stress in eating disorder**

The role of stress in eating disorders can be understood in terms of early intrauterine influences during the foetal stage of development which can lead to later risk of ED. Here, maternal stress such as depression, nutritional deprivation can lead to increased risk of several psychiatric disorders, addictions, obesity and other nutritional problems. There is also a specific risk of eating disorders due to maternal adversity as shown in the prospectively conducted Ice Storm study from Canada. Early childhood adversities including childhood abuse leads to altered stress response. The increased sensitivity of the HPA axis leads to a general increase in risk of psychopathology and specifically increases the risk of binge eating, bulimia and related eating disorders.

Among the more proximal risk factors for bulimia nervosa or binge eating disorder, the stress-relieving effects of “comfort foods” may be understood as the initial factor. When there are repeated episodes of stress or chronic stress, the prolonged consumption of high calorie foods for their stress relieving effects leads to (i) diet-induced obesity and (ii) a loss of the stress-relieving effects over time. The resultant obesity in turn leads to a more stressful state, thereby perpetuating a vicious cycle of stress and binge eating associated with mood dysregulation (depression and anxiety), propensity for addictive disorders and is associated with borderline personality traits and suicidal behaviour in some cases.

On the other hand, Anorexia Nervosa is characterised by a different paradigm of stress-induced restriction of food intake. This is more pronounced in females, explaining a female preponderance of this condition. Behavioural traits such as perfection, preference for orderliness, emotional constraint and behavioural inhibition are the background clinical risk factors in this group. The restriction of caloric intake acts as a precipitating factor to lead to the development of AN. Once AN develops, there are further epigenetic changes in several systems relating to hunger-satiety, mood and social behaviour which tends to maintain the restrictive food intake in this group of patients.

## **CONCLUSIONS**

There is sufficient evidence for the role of stress in the onset and maintenance of eating disorders. They range from distal factors occurring during foetal period, infancy and early childhood to more proximal factors such as food restriction and

social stress. The cycle of stress related food-restriction versus binge eating is different for restrictive eating disorders like AN versus bulimic disorders like BN or BED.

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## **STRESS AND ALCOHOL ADDICTION**

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### **OUTLINE**

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## **INTRODUCTION**

Stress is ubiquitous. Though stress can be defined in many ways, it has been broadly conceptualized as any stimulus that an organism perceives as harmful or distressing. Under the ambit of the terminology of stress, both physiological and mental stress, has been included. Under conditions of **physiological stress**, some physiological functioning or extraneous parameters are altered, leading to an adaptive change in the organism. Animal models have been developed for manipulation, quantification, and assessment of physiological stress. **Mental stress**, on the other hand, is a subjective experience of being affected by difficult life circumstances. Stress can be **acute or chronic**, i.e., occurring in a short span of time or over a long period of time. Stress has also been classified as **eustress**,

i.e., a stress that helps an organism/individual adapt better to the circumstances, or **distress**, i.e., a stress that is overwhelming or leads to poorer functioning. Excessive stress has been associated with the genesis of negative affect, anxiety, depression, and even post-traumatic stress syndromes.

Individuals use many means and mechanisms to alleviate stress. **Alcohol** has been used by many individuals to relieve stress. In fact, alcohol has been found to have a **stress response dampening (SRD) effect**, whereby the perception of stress is reduced as a consequence of alcohol use. However, alcohol consumption, as a regular method of coping, has its adverse consequences. The repertoire of behavioural, biological and psychological changes that occur with regular and increasing consumption of alcohol and the development of alcohol use disorders may accentuate stress. The association of alcohol use disorder and stress have been considered as quite complex.

If stress is ubiquitous, alcohol use and alcohol use disorders are fairly common. The typical course of alcohol addiction usually begins with the first episode of **alcohol intoxication** occurring in the adolescent period. This follows a period of **problem drinking or binge drinking**. The onset of an **alcohol use disorder** is usually observed in the early to mid 20s. The majority of alcohol-related disorders develop by the late 30s. **Withdrawal** in alcohol use disorders is seen after other aspects of alcohol use disorder, including craving and tolerance, have developed. Alcohol use disorder has a variable course that is characterized by periods of **remission** and **relapse**. A decision to stop drinking, often in response to a crisis, is usually followed by a period of abstinence, which often leads to limited periods of controlled or non-problematic drinking before a full blown relapse. However, once alcohol intake resumes, it is highly likely that consumption rapidly escalates to the previous drinking level. Alcohol dependence is associated with adverse familial, social, and occupational consequences. It is also associated with a significant increase in the risk of accidents, violence, and suicide.

Forays have been made to understand the relationship between stress and alcohol addiction, including animal and human research(Pohorecky, 1991; Sayette, 1999; Anthenelli, 2012; Fava et al., 2019). This chapter aims to provide a broad overview of the relationship between alcohol addiction and stress. The chapter initially discusses the role of the Hypothalamic Pituitary Adrenal (HPA) axis in the relationship between alcohol and stress. Subsequently, salient findings from

animal studies are discussed. The role of early life stressors and alcohol addiction, along with the role of stress in relapse to alcohol dependence, are presented. The potential role of handling stress in the therapeutics of alcohol use disorders is also discussed in the chapter.

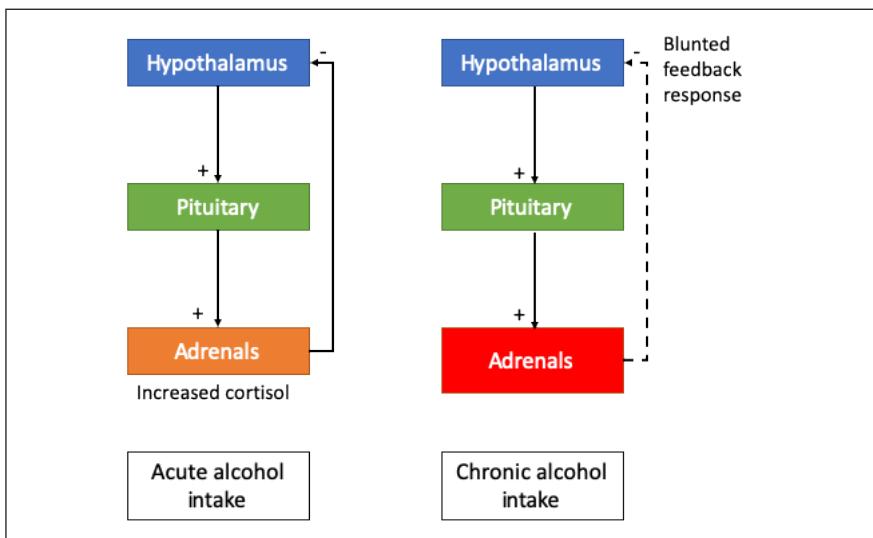
## HPA AXIS, STRESS, AND ALCOHOL ADDICTION

The biological response to stress primarily involves the HPA axis. Activation of the HPA axis leads to CRF-stimulated release of adrenocorticotropin (ACTH) from the anterior pituitary, which stimulates the release of cortisol from the adrenal glands(Agoglia and Herman, 2018). It also involves sympathetic and parasympathetic components of the autonomic nervous system. A healthy stress response is characterized by a quick rise in cortisol levels, followed by a rapid decline with the termination of the stressful event.

**Acute alcohol use**, directly and indirectly, stimulates the HPA axis increasing cortisol levels(Stephens & Wand, 2012), particularly if blood alcohol levels exceed 100 mg%. The onset of alcohol dependence is accompanied by bouts of elevated cortisol levels in the blood due to repeated cycles of acute alcohol intoxication and withdrawal. This leads to dysregulation of the HPA axis, causing attenuated cortisol reactivity in response to alcohol consumption. **Chronic alcohol use and acute alcohol withdrawal states** are associated with an increased secretion of the corticotropin-releasing factor (CRF), norepinephrine, and cortisol in the hypothalamus, amygdala, hippocampus, and prefrontal regions. **Abstinence** from alcohol (2 to 6 weeks) usually brings back the normal diurnal patterns of cortisol secretion. The acute and chronic effects of alcohol on the HPA Axis is shown in **figure 1**.

Both stress and alcohol use can lead to allostatic responses in body systems. **Allostasis** refers to the process through which various biological processes attempt to restore homeostasis when an organism is threatened by various types of stress in the internal or external environment. Allostatic responses can involve alterations in the HPA axis function, various signalling molecules, including the neurotransmitter systems, other components of the nervous system, or other body systems. Both stress and alcohol increase the allostatic burden on the body and create a state of reward dysregulation and maladaptive response to stress.

Figure 1: Effect of alcohol on Hypothalamic Pituitary Adrenal (HPA) axis



It has been hypothesized that **increased cortisol responsivity** may promote the transition to a dependent pattern of drinking in people who are at risk for developing alcohol dependence. This can occur due to cortisol's ability to promote **habit-based memory formation** and learning during alcohol intoxication, especially during states of heightened arousal. Moreover, wide fluctuations in cortisol secretion observed in alcohol-dependent individuals could help maintain these addictive behaviours. Persistent hypercortisolism may be toxic to neurons in the hippocampus. **Hippocampal damage** may result in alcohol-related symptoms such as personality changes, memory loss, and depression. Stress-induced elevation in cortisol may result in enhanced mesolimbic dopaminergic activity, through glucocorticoid receptors in nucleus accumbens and thereby regulating burst frequency of mesolimbic dopaminergic neurons; or through bidirectional organic cation transporter leading to increased extracellular dopamine, thus reinforcing alcohol-seeking behaviour.

The **prefrontal cortex** is involved in complex cognitive tasks, including assessing likelihood of reward or punishment during critical decision-making situations, as well as, assessing internal and external affective cues and responding adaptively, particularly in stressful situations. Psychosocial stress has been found to disrupt prefrontal cortex functioning in humans. This disruption has been partly

attributed to chronic exposure to elevated glucocorticoid levels causing neuronal degeneration and partly to physiological changes that occur as part of the overall stress response, such as increased catecholamine levels.

**Amygdala** is a major extrahypothalamic source of CRF-containing neurons that carry large numbers of CRF-1 and CRF-2 receptors. It has a primary role in the processing and memory of emotional reactions. It has been seen that the hypothalamic CRF system is important for modulating neuroendocrine responses to stress. In contrast, the extrahypothalamic CRF system manifests the behavioural response to stress via the amygdala and other limbic regions. Chronically elevated cortisol levels also increase CRF expression in the central amygdala, which contributes to anxiety-like behaviours. The heightened or exaggerated emotional and fearful reactivity to perceived stress leads to excessive alcohol drinking. This could also explain the perceived stressful situation as a trigger for relapse.

## ANIMAL STUDIES IN STRESS AND ALCOHOL ADDICTION

Animal studies offer a very useful paradigm for studying the relationship between alcohol and stress(Noori et al., 2014; Spanagel et al., 2014). The unique advantage of animal models is that their exposures can be manipulated in controlled experimental conditions. One does not have to wait for a human lifetime (or many years) to study a phenomenon of interest. Also, the information can be gleaned effectively and efficiently from the tissues of interest, including brain samples. This has helped to gather a deeper understanding of various forms of stress on the behavioural, physiological, neural, and neurochemical structure and function of animals exposed to alcohol. Animal models have been developed to mimic human behaviour, including models of alcohol addiction (like operant self-administration, free-choice home cage drinking, etc.) and stress (like foot shock stress, forced swim stress, white noise stress, chronic restraint stress, etc.). A caveat often applied to animal models that they do give behavioural and physiological information quite effectively, but cannot provide understanding of human subjective experience. Yet, animal models have provided a substantial literature base of neurobiological underpinnings of the relationship of stress and alcohol.

Apart from furthering the literature on the role of alcohol and stress on the HPA axis, animal studies have also provided insights into effect of other neurotransmitters. The rewarding effects of alcohol are mediated by the mesolimbic **dopaminergic circuit** (reward pathway) that comprises of dopaminergic neurons from the ventral

tegmental area of the brain stem to the nucleus accumbens (reward centre), part of the ventral striatum. The dopaminergic circuitry also includes the meso-cortico-limbic pathway involving the ventral tegmental area, prefrontal cortex, amygdala, nucleus accumbens, and hippocampus. Acute alcohol intake also increases synaptic dopamine activity via increased firing of dopamine cells in the ventral tegmental area and subsequent release of dopamine in the ventral striatum. However, **chronic alcohol consumption** creates a hypodopaminergic state that motivates further consumption of alcohol to restore the normal levels of dopamine.

Alcohol consumption **acutely** affects the **GABAergic neurotransmission** by increasing GABA release in various brain regions enhancing inhibitory effects of GABA neurotransmission. Decreased GABAergic tone is seen with **chronic alcohol use** and in alcohol withdrawal state. This results in a negative affective state of anxiety, dysphoria, and craving, which are transiently relieved by the resumption of alcohol consumption.

Preclinical studies have shown an increase in brain concentration of **serotonin** and serotonin metabolism on the administration of alcohol. Direct infusion of serotonin activates the dopaminergic neurons in the reward pathway. In contrast, **chronic exposure to alcohol** reduces serotonin concentration in the brain, which has been associated with impulsivity, aggression, and behavioural disinhibition. Animal studies have indicated that the brain's serotonin systems are also affected by the brain regions that mediate another stress-related reaction, the fear response. The association of the serotonin system with both addictive behaviours and anxiety states supports the notion that a neurobiological connection exists between stress and alcohol addiction.

Further research to elucidate the role of alcohol and stress in animal studies have also included evaluation of the role of  **$\mu$  and  $\kappa$  opioid receptors, neurokinins, cannabinoid 1 receptor, neuropeptide Y, and  $\alpha 1$  adrenoreceptor**.

Synthesis of preclinical studies have been done using cluster analysis and meta-analysis methodology. One of the salient findings has been that stress induced alcohol consumption is age-dependent. It has been found that adult animals are more susceptible to alcohol consumption after stress than adolescent animals. Stress has generally not been found to enhance alcohol intake in the operant conditioning model but has been found to increase consumption in the **free choice**

**home cage drinking model.** The type of stress also has a role in determining the increase in alcohol intake after stress. It has been seen that **foot shock stress and forced swim stress** have been associated with increased alcohol intake, while **restraint stress** is not associated with an increase in alcohol intake. Among the stress patterns (chronic and acute stress), chronic stress was associated with greater alcohol consumptions, though the difference from acute stress seems to be modest. These thematic inferences have considerable translational value, as not only the context of alcohol determines the extent of alcohol intake after stress, but so does the nature, pattern, intensity, and time course of the stress.

## **EARLY LIFE STRESSORS AND ALCOHOL USE**

Early life stressors have been reported to be associated with the initiation of alcohol use (Enoch, 2011). Epidemiological studies have shown that adverse childhood experiences are highly predictive of earlier onset of alcohol use and the development of alcohol dependence in adolescents. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study(Hasin & Grant, 2015) showed that experiencing two or more childhood stressful life events compared with none, significantly increased the risk for alcohol dependence after controlling for socio-demographic and other variables. Similarly, the U.S. National Longitudinal Study of Adolescent Health (AddHealth)(2016) found that childhood maltreatment at age less than 11years had resulted in an increased the risk for adolescent binge drinking, even after controlling for age, sex, ethnicity, monitoring, and parental alcoholism. This suggests that adverse life events in childhood are associated with the development of alcohol use disorders.

The confounders expected in such an association are genetic vulnerability (alcohol use disorders in parents is likely to increase the chances of alcohol use disorder in the offspring), and the stressful family environment when one or both of the parents have alcohol use disorders. The presence of **early life stressors** is associated with increased risk for alcohol use and the development of alcohol use disorder in early adulthood that is independent of family history.

**Animal models** have also been developed to study impact of early life stress and development of alcohol use disorders. It has been seen that early life stress can result in permanent neurohormonal and HPA axis changes, brain morphological changes brain and gene expression changes in the mesolimbic dopamine reward pathway thus, increasing vulnerability to addiction.

The neurobiological research has shown that the adolescent brain undergoes maturational changes at a variable pace in different brain systems. The subcortical reward and emotion circuitry mature earlier and is followed by subsequent maturation of prefrontal control circuitry. This creates an imbalance in cognitive and emotional regulation of behaviour. It results in an increased reactivity to novel, rewarding, or emotional stimuli during adolescence and promotes high-risk behaviours, including alcohol consumption, binge drinking, and drunk driving. The presence of stressors during adolescence further increases the risk for problematic alcohol use by disrupting the reward circuit function. Adolescents are also more vulnerable to stressors due to **prefrontal cortex remodelling**. It has been demonstrated that adverse childhood experiences before age 11 are positively associated with externalizing behaviours at ages 12–14 years, which in turn is positively associated with problematic alcohol use at ages 15–17(Fava et al., 2019).

## **GENDER DIFFERENCES IN RELATIONSHIP OF ALCOHOL AND STRESS**

Differences have been found in the impact of stress on alcohol use among males and females (Retson et al., 2016; Logrip et al., 2018). This has been borne out from the findings of preclinical and human studies. A study by Pedrelli et al.,(2016) of older adolescents has found that severity of depressive symptoms was associated with earlier onset of alcohol use, more frequent alcohol consumption, and occurrence of intoxication in both males and females. However, the relationship of early drinking onset and presence of depressive symptoms was higher among females as compared to males. Among adults, women having two or more stressful life events in the past year were 4 times more likely to develop alcohol use disorder compared to men with two or more past year stressful life events who had 2.5 times likelihood of developing an alcohol use disorder (Verplaetse et al., 2018).

Women have also been found to have relapse to alcohol use as a consequence of stressful life event more commonly than men (Becker & Koob, 2016). Psychiatric illnesses such as post-traumatic stress disorder (PTSD), depression and anxiety disorders are strongly associated with alcohol use disorders, and this association seems to be stronger in women as compared to men. This suggests that the relationship of stress related negative affect and alcohol consumption is much more prominent in women as compared to men. Early life stressors also seem to operate differently in males and females with regards to development of alcohol use

disorders and problematic drinking. Women endorsing a history of maltreatment before 18 years of age display more vulnerability to alcohol-related issues. It has been observed that sexual abuse, emotional abuse and emotional neglect were more likely to be associated with increased rates of alcohol use disorders in women compared to men (Peltier et al., 2019).

Sex differences in effect of stress on alcohol consumption has been noted in **animal studies** as well. It has been seen that in animal models of PTSD, female rodents are more likely to increase alcohol consumption compared to males. The noradrenergic system has been implicated in reinstatement of alcohol consumption behaviour with stress after a period of extinction. It has been observed that yohimbine, an  $\alpha$ -antagonist and pharmacologic stressor that enhances the noradrenergic activity, can lead to reinstatement of alcohol-seeking in rodents, particularly so in female rodents as compared to males. Looking at the interaction with HPA axis, corticosterone exposure during adolescence has been found to sensitize rodents to stress-induced consumption of alcohol later in life. It has been found that adolescent female rodents who were exposed to corticosterone were more sensitive to yohimbine-induced reinstatement of alcohol-seeking during adulthood. These findings suggest again that stressful situation related alcohol use may be more common in females than males (Becker & Koob, 2016).

## **STRESS AND RELAPSE TO ALCOHOL USE**

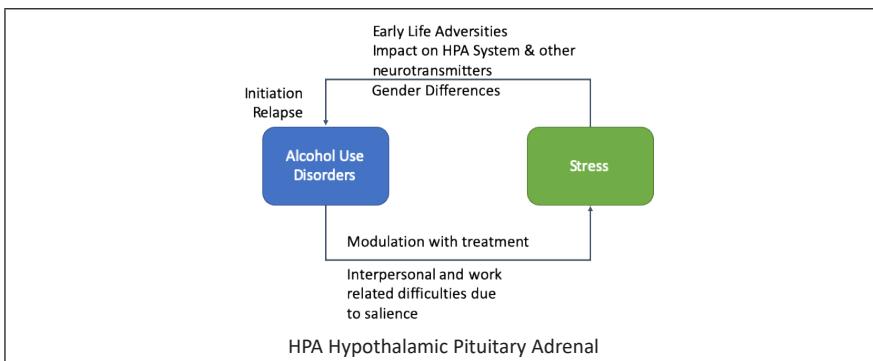
Presence of high levels of stress and craving in early recovery in alcohol dependent individuals is predictive of poorer treatment outcomes (Blaine et al., 2016). Early abstinence from alcohol is associated with higher levels of anxiety when exposed to alcohol cues, greater emotional distress, and increased stress- and alcohol cue-induced craving. These states are accompanied by disruption in normal functioning of the peripheral stress pathways, including the HPA axis and the autonomic components, which are involved in mobilizing the body for action during stress but also in physiological regulation of the stress response. A lack of normal stress regulation during this early abstinence period leaves the individual vulnerable to increased craving, anxiety, and risk of relapse, particularly under stressful conditionsFollow-up studies have found that those individuals who relapsed within 3 months of treatment for alcohol use disorders were more likely to have severe stress before entering treatment as compared to those who were abstinent. Experimental evidence suggests that stress can provoke relapse-like behaviour and increase alcohol drinking more easily in subjects with a history of dependence.

**Preclinical studies** have shown that animals exhibit increased stress responsiveness following withdrawal from chronic alcohol exposure. This has been measured by several experimental procedures that provoke behavioural measures of stress/anxiety, such as reduced social interaction in a novel environment, reduced exploration in threatening circumstances, and greater electroshock-induced suppression of ongoing behaviour.

Similar findings have been observed in **human studies**. Stress-induced alcohol craving in the laboratory during inpatient treatment was predictive of number of days of alcohol used and total number of drinks consumed during the 90-day follow-up period. High levels of stress- and **cue-induced anxiety** are associated with less follow-up in aftercare during the recovery period. Exposure to stress imagery in patients with alcohol dependence showed persistent increase in alcohol craving, subjective distress, and blood pressure responses across multiple time points compared with social drinkers. This suggests an inability to regulate emotional stress in patients with alcohol dependence. Thus, while chronic alcohol exposure and withdrawal experiences lead to disturbances in homeostatic regulation of HPA axis function, **behavioural sensitization to stress** makes individuals more vulnerable to relapse and return to uncontrolled, harmful levels of alcohol consumption.

Extending these findings, **attenuated cortisol responses** in those with alcohol use disorders were more likely to relapse. Studies have shown that patients with alcohol use disorders who also had attenuated stress responses were more likely to relapse, and even during abstinence, a blunting of the stress response was seen. This blunting of stress response gradually improves with time. Alcohol addiction and stress are interlinked in many ways (schematically shown in figure 2).

Figure 2: Relationship of stress and alcohol



## MANAGING STRESS IN ALCOHOL ADDICTION THERAPEUTICS

### Stress as a reason for treatment initiation

Clinically, it has been seen that stressful life situations consequent to alcohol use bring patients with alcohol use disorders to treatment (Brady & Sonne, 1999). It has been seen that individuals with alcohol use disorder who sought treatment were more likely to perceive their drinking problems as more severe and had experienced more stressors and more **negative life events**. These stressors which brought patients with alcohol use disorders include **both chronic issues** (like marriage or employment problems) and **acute events** (like divorce or accidents) that are often associated with alcohol consumption (Sygit-Kowalkowska & Ziolkowski, 2019). One must acknowledge that **subjectivity exists in appraisal of stress**, and studies are constrained in the recollection of stressful events prior to enrolment into treatment programs. But these treatment studies do suggest that patients with personal resources like employment and intact marriage are likely to enter treatment more quickly than those without these resources. Possibly, those with more social contacts and functional responsibilities are likely to be suggested to seek treatment for the problems.

### Pharmacotherapy

Alcohol use disorders often co-occur with other psychiatric disorders, including anxiety and depression, wherein stress plays an important role in genesis and perpetuation. Thus, adept pharmacotherapy addressing stress and related conditions may theoretically help to prevent relapse. The **dopaminergic system**, in conjunction with the **opioidergic system** plays a role in the genesis of alcohol dependence in addition to stress modulated HPA. Thus, **opioid antagonist naltrexone** and **selective serotonin reuptake inhibitors** may play a role in the prevention of drinking under stressful conditions. Animal studies have shown that naltrexone, an opioid antagonist, prevented increased drinking after stressful situation. In another study among primates, sertraline has been shown to reduce alcohol consumption and aggression after stressful situation (but not extremely stressful situations). Thus, medications may have some role in moderating drinking outcomes after stressful situations, but this needs to be further studied in humans.

### **Psychotherapy**

Psychosocial therapies, including psychotherapy, are one of the important treatment approaches for patients with alcohol use disorders. Typically these therapies incorporate elements of relapse prevention. Identification of stressful situations that trigger craving and ways of dealing with such craving without resuming alcohol use is the focus of some of these therapies. Thus, clinicians recognize the role of stressful situations in perpetuating alcohol use disorders, and collaborative attempts are encouraged to anticipate, avoid, and deal with these situations. Coping skills enhancement and problem-solving skills are specific therapy elements that involve dealing better with stress. Enhancing social support systems through **Alcoholics Anonymous** also is an approach that attempts to provide better opportunities to mitigate stress that leads to relapse. As lower stress management skills have been shown to be linked to relapses, clinical endeavours aim to reduce the genesis of stress, and handle stress better as situations arise.

## **CONCLUSIONS**

Alcohol addiction and stress are interlinked in many ways. Stress, including that due to early life adversities, plays a role in the occurrence of alcohol use disorders. Stress also results in treatment-seeking for alcohol use disorders. On the other hand, the development of alcohol use disorders leads to physiological changes that mimic a chronic stress situation. Treatment of alcohol use disorders also focuses on managing stressful life situations to prevent a relapse. Many insights have been gained from the animal experiments. Further research, especially human research, is required to elucidate the role of different kinds of stressors in accentuating, perpetuating, and remedying alcohol use disorders. A greater understanding of the relationship between alcohol use disorders and stress is likely to improve outcomes of patients with alcohol use disorders by providing management directions, including those of specific pharmacotherapies and psychosocial interventions.

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## **STRESS AND TOBACCO ADDICTION**

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### **OUTLINE**

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| 3. STRESS AND TOBACCO USE<br>INITIATION  | 4. TOBACCO ADDICTION MAINTENANCE<br>AND ASSOCIATION WITH STRESS                                   |
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| 9. MANAGEMENT OF TOBACCO<br>ADDICTION IN THE CONTEXT TO<br>STRESS – 'HANDLING ONESELF' | 10. CONCLUSIONS AND FUTURE<br>DIRECTIONS – 'LOOKING FORWARD'                                      |

### **INTRODUCTION: LIGHTING IT UP ABOUT 'LIGHTING UP'**

The world is currently fighting two pandemics – the ‘new’ COVID-19 and the ‘old’ tobacco pandemic which kills about 8 million people a year as per World Health Organization. It is not surprising that the two common attributes of our life namely tobacco and stress are interrelated. However, the much-touted belief and advertisement that tobacco reduces ‘stress’ is a myth and the fact remains that stress plays a contributing role to the initiation, maintenance and relapse. The

relationship between stress and tobacco use is bidirectional which is moderated by sex, emotional dispositions and adverse life events. Among the different psychiatric illnesses, the prevalence of tobacco use is twice the general population. Stress and tobacco use have a bidirectional relationship in the context of depression and post-traumatic stress disorder. For anxiety disorders, smoking leads to activation of brain stress systems which leads to increased risk of development of anxiety disorders whereas amongst schizophrenia with smoking, the poor stress coping leads to frequent relapses. In the current scenario stress, tobacco and COVID-19 may be an ‘unholy triad’ and E-cigarettes may not be very different from tobacco cigarettes when it comes to relationship with stress, but currently there is very little scientific literature to reach a definite conclusion. Overall, considering the intimate relationship between stress and tobacco use – stress management is part of almost all interventions for tobacco or smoking cessation.

Since March 2020 the World Health Organization has declared Covid-19 is a pandemic. However, not many of us know that WHO has classified the alarming trends of tobacco use and its serious health consequences around the world as a pandemic (Taylor, 1996) for the last few decades. Tobacco is available in different forms (see table I). As per WHO, in 2016 over 1 billion individuals above 15 years of age smoked tobacco and smokeless tobacco is consumed by more than 300 million people worldwide(Siddiqi *et al.*, 2020). The worldwide deaths due to tobacco numbered 8 million per year with the low- and middle-income countries being more affected than high income countries (World Health Organization, 2019). The often-quoted fact that women use tobacco less than men do is changing and it has been noted that mortality is earlier and more frequent in women using tobacco.

The study on global burden of disease for tobacco related illness has highlighted many disparities across the 195 countries and regions that were surveyed. The age standardized prevalence rates ranged from 4 - 47% for men and 1 - 44% for women. It was also noted that those who commence nicotine use earlier on continue the use till later on in life (Maciosek *et al.*, 2006). In the past century, 100 million persons died on account of tobacco use who could stop reducing their risks of dying from tobacco related illness (Anthonisen *et al.*, 2005). From the healthcare perspective, one of the most effective strategies would be to screen all persons for use and offer counselling and pharmacotherapy towards tobacco cessation(Maciosek *et al.*, 2006). Cessation is beneficial for all smokers across all ages (Rigotti, 2002). Cessation continues to be beneficial even when a tobacco

related illness has developed. About half of all the smokers may prematurely die of a tobacco related illness (World Health Organization, 2011). Smoking cessation has a definite mortality benefit for both men and women of all ages with greater gains at younger ages.

**Table 1. Forms of Tobacco Use**

Combustible tobacco (Smoked)	
Cigarette	Most commonly used Shredded tobacco leaves are rolled in a filter paper and lit at one end
Cigar	Do not have filters and are capable of delivering up to 3 - 5 times the nicotine smoked from a cigarette
Beedi (commonly used in South Asia)	
Hookah (Water pipes)	Devices that allow for smoke from lit tobacco leaves to pass bubbles up through water which is supposed to act as a filter. The air cured tobacco suited for such use is known to increase the risk for esophageal cancers manifold
Kretek (Clove cigarettes)	Rolled up tobacco leaves mixed with clove and sometimes other spices
Non-combustible tobacco (Smokeless)	
Chewing tobacco	Chew: Shredded tobacco leaves often sweetened and flavoured available as loose leaf, held tight in mouth between the gum and cheek  Guthka: A packaged premixture of crushed betel nut and tobacco along with sweeteners and flavours  Snuff: Dry, finely ground tobacco product placed in the nostrils and inhaled.  Moist snuff: Held in mouth similar to chewing tobacco  Misri: Also known as "Creamy Snuff" is a tobacco paste mixed with clove oil, spearmint, glycerin, menthol and camphor sold in toothpaste tube to women in India  Snus: Premixed sachets, held in mouth for absorption but no need for spitting
Dissolvable tobacco	Edible tobacco strips, sticks or orbs
Electronic nicotine delivery systems (ENDS)	Comprises a cartridge containing a nicotine rich liquid, an atomiser, a vaporisation chamber, a heating element and a battery  e-cigarettes  First Generation - Disposable (called "Cigalites")  Later generations - Personalised vaporisers (rechargeable batteries, up to 7000 flavourings)
Heat not burn tobacco products	Deliver inhalable nicotine rich smoke without combustion by heating the tobacco to temperatures lesser than what burns

Stress is too complex to lend itself to a single consensual description as has been discussed in other chapters (for a conceptual understanding see Part I). For the purpose of this chapter, the following definition of stress is appropriate - ‘an internal state which can be caused by physical demands of the body or by environmental and social situations which are evaluated as potentially harmful, uncontrollable or exceeding our resources for coping’. The physical, environmental and social causes of the stress state are called stressors(Morgan et al., 2006). This chapter provides a conceptualization of how psychosocial stress and tobacco use interact with each other. Here, ‘stress’ denotes ‘psychosocial stress’ and molecular, cellular, laboratory aspects and details of biological stress..

## PATOPHYSIOLOGICAL RELATIONSHIP BETWEEN TOBACCO AND STRESS: ‘Chicken or the Egg’ problem

Stress and stress related processes play an important role in our conceptualization of mechanisms at play during initiation, abstinence as well as relapse of tobacco use. Stress related mechanisms have been proposed by several authors and its constructs have been extended to explain addiction by many( Kwako & Koob, 2017). Some of the models and their applications have been summarized in Table 2 with respect to the influence they may have on tobacco use. These models have been constructed based upon preclinical/animal research which have been validated in clinical research involving human subjects.

**Table 2. Conceptualization of Models of Stress and Implications on Tobacco Use**

Model Name	Stress Diathesis Model (Monroe and Simons, 1991)	Transactional Model (Lazarus and Cohen, 1977)	Biopsychosocial Model (Engel, 1977)	Allostatic Model (Koob and Schulkin, 2019)	Differential Susceptibility Model (Belsky and Pluess, 2009)
Concept	Dispositional or vulnerability factors mediate impact of adverse events on risk of psychopathology or health problems	Impact of a stressful event is determined by properties of the situation as well as his perception of it and on the nature of his coping	Interaction of multiple influences (psychological/biological/social) lead to increasing risk of health or behavioural problems	Stressful events are dealt with by neuroendocrine adaptation. Chronic adaptation leads to dysregulation in physiological processes (Allostatic Load)	Some individuals are affected more than others by both negative and positive contextual conditions

Application to tobacco use	Adverse life events may contribute to initiation/maintenance/relapse of tobacco smoking behaviour	Tobacco smoking as a behavioural method used to cope with stress and negative affect	Psychological factors (stress, emotional status) along with biological factors (pharmacological effects of nicotine) and social factors (peers, modelling etc.) influence tobacco use	Allostatic changes influence substance use disorders by impacting hedonic reward systems and drive substance seeking within the construct of negative reinforcement	Environmentally sensitive, lead the healthiest lifestyle in the healthiest environments but also lead the unhealthiest lifestyles in the least healthy social environments
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### Preclinical Studies

Animal models have been constructed mainly to mimic the three major stages of intoxication, withdrawal and relapse. Intoxication and withdrawal is shown by deprivation model and relapse is mimicked by reinstatement models. In these models the different stages have been extensively modified by the different application of neuromodulators like CRF, corticosterone, etc. intransgenic models with optogenetics and chemogenetics.

A microdialysis study (Enrico *et al.*, 2013) in rats found that stress attenuated the rewarding properties of nicotine and this effect was reversed upon the administration of a corticosterone (CORT) synthesis inhibitor and a glucocorticoid receptor antagonist, indicating that the attenuated dopamine response is mediated through CORT. A study in rats (Buczek *et al.*, 1999) demonstrated that the stress induced reinstatement wasn't universal for rewarding stimuli but for nicotine and stress reinstates nicotine seeking behaviours through the increase in stress response system(Zislis *et al.*, 2007).

Cross sensitization study (Johnson *et al.*, 1995) done in rats to study nicotine and stress, revealed that stress was necessary for expression of nicotine sensitization and was found to augment the behavioural responses to nicotine, thereby increasing the vulnerability for developing its addiction. These animal studies help to explain why stress elevates smoking behaviour in humans and how increased smoking may reflect reduced reward and satisfaction, despite self-reported elevations in smoking

satisfaction following stress. The maintenance of nicotine seeking behaviour can be explained by the alterations caused by stress, increasing the behavioural responses due to cross sensitization while also attenuating the rewarding properties of nicotine.

### Clinical Studies

The studies investigating the associations of stress with tobacco addiction have predominantly researched the use of cigarette smoking whereas smokeless tobacco has taken a back-seat. The early literature was based on self-reports( Wills et al., 2002) and retrospective study designs(Turner et al., 1998). Recent study designs combine self-report and biological markers of stress helping discover the mediators and moderators of the relationship between stress and smoking. The HPA axis response and autonomic nervous system have been studied for the role of acute and chronic stress in various stages of tobacco addiction.

## STRESS AND TOBACCO USE INITIATION

Effects of nicotine on the HPA axis in the body leads to an increase in the activation of the stress response (Rohleder & Kirschbaum, 2006) which may be dose dependent(Gilbert et al., 2000) and involve the activation of the autonomic nervous system leading to a surge in catecholamines and an increase in the cardiovascular response. The brain stress response system is affected by the activation of nicotinic acetylcholinergic receptors (nAChR's)(Fagen et al., 2003) in the mesolimbic pathways. The activation of dopamine receptors in the reward pathways is mediated indirectly by the glutamatergic transmission leading to secondary dopaminergic release. These structures are also activated during physiological stress. Thus, it can be concluded that stress activates the brain stress as well as reward pathways. Nicotine may be conceptualized to be a neural substrate upon which promotes acute stress to induce craving, thus enhancing the reinforcing effects(Sinha, 2008).

The findings from human studies, albeit methodological limitations, suggest that decreased HPA axis reactivity in pre-adolescent period serves as a risk factor for smoking initiation(Moss et al., 1999) whereas increased reactivity during adolescent period has been associated with increased smoking behaviour(Rao et al., 2009).

**Box 1: Stress Response and Initiation of Tobacco Use**

- The effects of nicotine and acute stress are same in the body
- Nicotine may serve as a neural substrate by which acute stress primes craving and enhances the reinforcing effects of nicotine

**TOBACCO ADDICTION MAINTENANCE AND ASSOCIATION WITH STRESS**

One of the most common reasons for maintenance of tobacco use has been suggested to be ‘stress relief’. The sense of relief perceived by smoking tobacco is due to a reversal of the nicotine deprived negative mood state. Subjective stress levels are found to decrease immediately after smoking, while they remain higher between two time-points of tobacco consumption.

The regular tobacco smokers had an increased basal cortisol level(Kirschbaum et al., 1992). Chronic consumption of tobacco smoke was associated with a decrease in the reactivity of cortisol levels to stress suggesting that the impairments in other adaptive coping skills of an individual during stressful period tends to facilitate their overreliance on tobacco in suppressing the cortisol surge(Richards et al., 2011).

**Box 2. Stress Response as a Factor for Tobacco Use Maintenance**

- Habitual smokers have higher baseline cortisol levels
- Higher baseline levels mean less reactivity to stressful situations
- Tobacco is substituted as a coping mechanism to cope with acute stress

**TOBACCO ADDICTION WITHDRAWAL, RELAPSE AND ASSOCIATION WITH STRESS**

Stress is a prominent trigger found in individuals with relapse. Abstinent individuals under stress increase their frequency of tobacco use which hastens their evolution to full relapse. Relapse under stress may be due to a decreased ability to resist smoking cigarettes(McKee et al., 2011). The symptoms of withdrawal are often distressing that lead to a heightened experience of stress and increase the probability of smoking again.

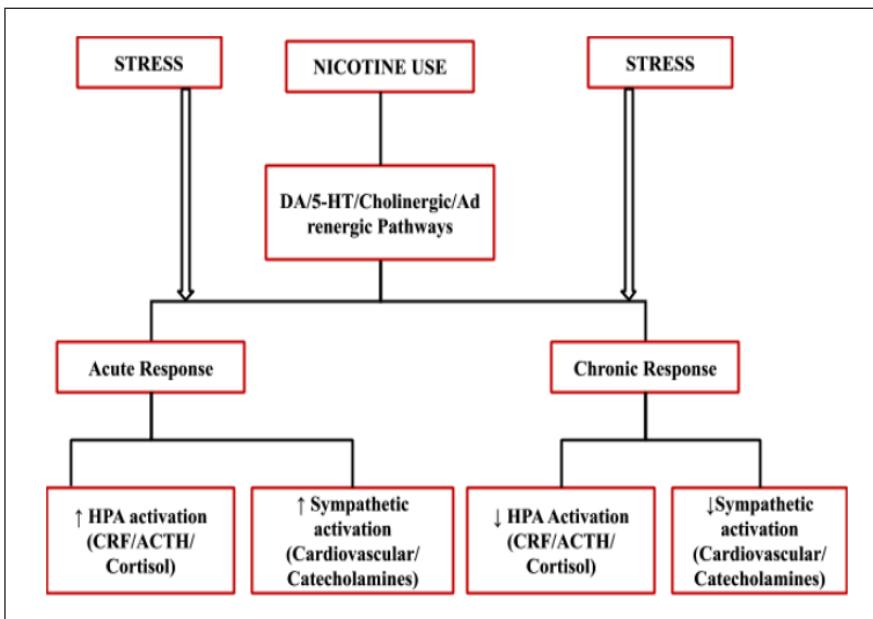
**Box 3. Stress Response as Factor for Relapse in Tobacco Addiction**

- Abstinence has a stress like effect on tobacco dependent users
- Dysregulation of stress response could be associated with long term smoking
- Decreased HPA axis response to stress may be a predictor of relapse

Short term abstinence (18 hours) of smoking indicated an exaggerated stress response. Acute stressful situations in chronic users (whether actively smoking or abstinent) showed attenuated autonomic responses compared to non-users which demonstrate that chronic exposure to tobacco blunts the stress response (al'Absi, 2018). In abstinence, the relapse in the first week was characterized by greater craving and overall distress on the first day compared to those who remained abstinent over the same period. Greater decline in the cortisol levels were detected during the abstinent day compared to when they smoked again with no change in diurnal variation (al'Absi et al., 2004) which may be enhancing the reinforcing value of smoke after abstinence driven by the motivation to self-medicate, contributing to early relapse (Piasecki et al., 2003). Relapse over a four-week period was predicted when attenuated ACTH levels and blood pressure responses to stress were found (al'Absi et al., 2005). This dysregulated stress response system is key to understanding the vulnerability for smoking relapse.

There is another anomalous segment of individuals known as **chippers**, with chronic use but not experiencing withdrawal and minimal or no addiction to tobacco. They do not consume to relieve their stress or associated negative affect(Shiffman, 1989) and seem to have less first dose dizziness or aversion to cigarettes. The overall heuristic depiction between stress and tobacco addiction may be summarized as in Figure 1. Hence it can be said that it is definitely not stress that leads to tobacco use always – it is rather bidirectional with tobacco causing significant dysregulation to the stress response systems.

**Figure 1. A Heuristic Model depicting effects of Nicotine use on HPA and Sympathetic Systems**



Several moderators may play a role for the dysregulated response in those with tobacco addiction.

**Table 3. Moderators of Stress Response in Tobacco Addiction**

Sex	<ul style="list-style-type: none"> <li>Hormonal and cardiovascular responses to stress vary between sexes</li> <li>Females cite stress experience more often, leading to lapse and relapse</li> <li>Females more likely to use tobacco as a coping mechanism than males</li> <li>Females are observed to be less likely to maintain long term abstinence</li> <li>Psychological markers predict relapse better in females</li> <li>Biological markers predict relapse better in males</li> </ul>
Emotional Dispositions	<ul style="list-style-type: none"> <li>High trait level hostility in tobacco users who use it to cope with stress</li> <li>High anger levels in these people during withdrawal and stress response</li> <li>These may contribute to initial substance use as well as relapse</li> </ul>

**Adverse Life Events**

- Adverse childhood events linked to lifetime prevalence of substance use as well as long term effects of stress
- Prospective research shows adverse life events increase challenges during abstinence
- Highlight a vulnerability to relapse.

## **TOBACCO ADDICTION AND STRESS ASSOCIATED PSYCHIATRIC DISORDERS – *THE UNHOLY ‘TRIANGLE’***

There is evidence to suggest that the rates of smoking tobacco amongst those suffering from depression, post-traumatic stress disorder and other anxiety disorders are almost twice that of the general population( Lawrence et al., 2009). Those with a history of mental illness are more vulnerable at times of stress and negative affect, to relapse back.

### **Depression**

There was an increase in habit size, decreased duration of abstinence compared to non-depressed individuals. Smoking was seen to affect the quit rates. A systematic review and meta-analysis(Hitsman et al., 2013) showed that those with a history of prior major depressive episodes had 17% lower odds of achieving short term abstinence and 19% lower odds of achieving long term abstinence compared to those without a history of the same. Notable factors affecting abstinence were found to the view that smoking helped them relieve negative affect, increased sensitivity to smoking related cues(Weinberger et al., 2012) and decreased confidence to resist smoking in a range of situations (John et al., 2004). Smokers who did not have a history of depression prior to initiation, are at risk of depression than those who do not smoke. Depression also poses barriers to smoking cessation and increases the risk of relapse.(Weinberger et al., 2017)

### **Post-Traumatic Stress Disorder (PTSD)**

Smokers were approximately twice more likely to have PTSD than nonsmokers in the general population, and individuals with PTSD were approximately twice as likely to be current smokers. Smokers with PTSD were more likely to relapse in their first week due to negative affect and trauma reminders (Beckham et al., 2013) and would have higher relapse rates. PTSD symptoms were associated with expectations that smoking would reduce negative affect, which, in turn, was associated with increased smoking rate and nicotine addiction (Dedert et al., 2012). Male sex was associated with nicotine addiction and PTSD avoidance, while the

relationship between PTSD and smoking relapse due to withdrawal was stronger in females (Kearns et al., 2018).

### **Schizophrenia**

A higher rate of smoking compared to the general population is seen in patients with schizophrenia. A largely accepted view of this was the self-medication hypothesis which has recently been found to be short of some explanations (Manzella et al., 2015) and currently the underlying vulnerability hypothesis has taken the center-stage (Wing et al., 2012). Hence, though the initiation occurs due to the predetermined neurophysiological, genetic and neuropsychological reasons, thereafter the maintenance occurs to cope with stress (Esterberg & Compton, 2005). A higher rate being partly due to a lack of other effective ways in dealing with the social stigma of their illness and inability to control the associated perceived stress.

### **Attention Deficit Hyperactivity Disorder (ADHD)**

The associations between stress, ADHD and tobacco smoking has not been studied extensively although there are propositions that substance use and tobacco smoking are linked. A large cohort prospective study found out that stress and ADHD were independent contributors to tobacco use. They appear to have distinct pathways and there is no interaction between stress and ADHD per se (Galéra et al., 2017). However, this arena is still short of conclusive research.

## **TOBACCO ADDICTION, STRESS AND SPECIAL POPULATIONS - ARE THERE 'RISK' GROUPS?**

### **Adolescents**

About 90% of adult smokers initiate smoking in adolescence. The younger an individual is when he/she begins smoking, the greater is the increased risk for tobacco addiction later in life (Chen & Millar, 1998). Stress was found to be a risk factor for initiating tobacco use and playing a role in the mediation of the decision to start smoking in previously non-smoking adolescents (Byrne et al., 1995). A longitudinal study has shown that higher perceived stress during adolescence was associated with an increased risk of smoking initiation or maintenance at one-year follow-up with odds ratio of 1.05 (Finkelstein et al., 2006). Both stress and tobacco use/nicotine use cause long term changes in the brain when experienced during adolescence. The early onset places them at a risk of developing addiction, increased severity of addiction as well as being less likely to quit (Holliday and

Gould, 2016). There is a dearth of prospective studies on adolescents and the impact of stress on their tobacco/nicotine use. The increase in rewarding effects of tobacco as well as risk of not developing adequate effective positive coping mechanisms to deal with stress makes it imperative that they are studied and effective measures are developed to tackle them.

### **Women**

Stressful events have been reported to be the reason for initiation of tobacco use in women( Green, 2006). The maintenance of tobacco use behavior has been reported to be due to relatively higher distress experienced during stressful times and women using tobacco as a coping mechanism (Dicken, 1978). The greater experience of withdrawal effects and sensitivity to distress after tobacco use related cues make it less likely for them to maintain long term abstinence(al'Absi, 2018). Episodes of infant crying and irritability have been cited as triggers for tobacco-use in mothers who previously smoked tobacco, leading to relapse(Correa et al., 2015). This is a particularly important construct when dealing with cessation services during pregnancy and perinatal period.

## **OTHER ASPECTS OF STRESS AND TOBACCO ADDICTION**

### **E-cigarettes**

A recent add-on has been the electronic cigarette or e-cigarette which is an electronic nicotine delivery system. Once activated, the atomiser heats and vaporises the liquid in the cartridge which is then pushed into the vaporisation chamber as an aerosol then inhaled as a vapour - ‘vaping’(Hartmann-Boyce et al., 2018). The advent of e-cigarettes was touted as a solution to the health risks with tobacco use, that there would be no exposure to the many toxins and carcinogens. However, this has not borne out in research and WHO has issued a caution about its indiscriminate usage. A systematic review found that acute as well as chronic use leads to sympatho-excitatory effects which may be lesser than that caused by tobacco cigarettes but significantly higher than what is observed in non-smokers(Garcia et al., 2020). This may lead to alterations in the HPA axis and other brain stress response systems which needs to be researched in the future.

### **Perceived stress and tobacco addiction**

‘Perceived stress’ can be defined as feelings or thoughts that an individual has about how much stress they are under, as well as feelings about the uncontrollability and unpredictability of one’s life, how often one has to deal with irritating hassles, how

much change is occurring in one's life, and confidence in one's ability to deal with problems or difficulties (Phillips et al., 2013). Perceived stress is associated with higher tobacco smoking rates in high income as well as low-income countries as found by a multi-nation study. In those with high perceived stress, there was likelihood of having greater negative reinforcement related smoking expectations which may end up perpetuating the tobacco use into tobacco addiction (Stubbs et al., 2017). This must also be viewed as a barrier to prevention of tobacco initiation as well as tobacco cessation services.

### **Covid-19, stress and tobacco addiction**

COVID-19 pandemic appeared to have associated stress that affected tobacco smokers in different ways. It was observed that there was an increase in some tobacco users whereas a reduction in some. Reasons to stimulate their use was found to be boredom and restrictions in movement. The threats of contracting COVID-19 and getting severely ill may have been a reason for some to reduce their consumption (Bommele et al., 2020). It highlights the importance of providing greater resources for cessation services and the importance of creating public campaigns to enhance cessation in such dramatic times. Studies are currently undergoing to ascertain the effects of such a pandemic on the perceived stress and its impact on tobacco addiction.

## **MANAGEMENT OF TOBACCO ADDICTION IN THE CONTEXT TO STRESS – ‘HANDLING ONESELF’**

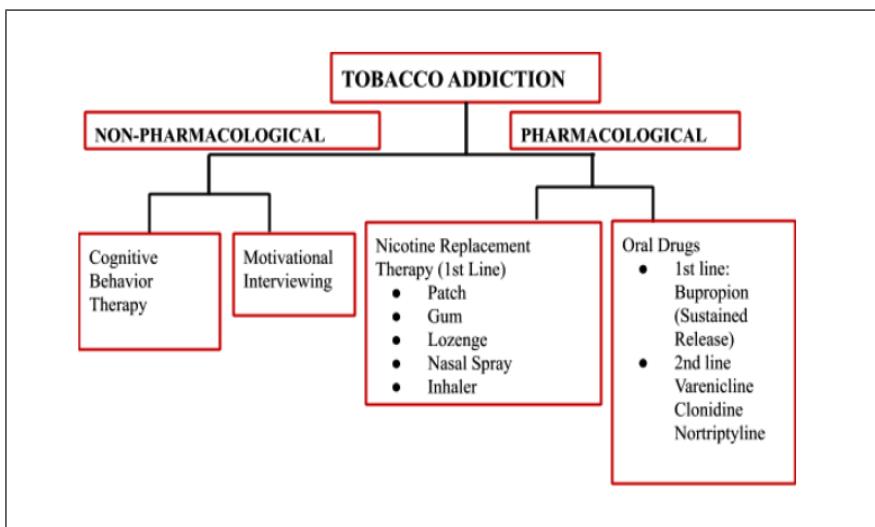
An overview for the general management of tobacco addiction has been described in Figure 2. Specific treatments for stress mediated factors in tobacco addiction are under research. Corticotropin releasing hormone 1 antagonists are being tested in animal studies(Karasavva, 2019), alpha 1 adrenergic receptor antagonist doxazosin has been tested in a small sample size human trial for stress precipitated smoking behavior (Verplaetse et al., 2017) and alpha 2 adrenergic receptor agonist guanfacine in modest sample sized study has been researched with some success (McKee et al., 2015). The overall translation of results from animal studies to human trials is still underway.

A meta-analysis (Prochaska et al., 2004) found psychosocial interventions in tobacco addiction to be effective in short term as well as long term. Cognitive behavior therapy that is tailor made for substance use disorders include several

measures for stress management like relaxation, regulation of emotions, tolerance to distress and improving coping skills which altogether improve the outcomes of stress induced substance use (Fronk et al., 2020). A meta-analysis(Goldberg et al., 2018) showed that mindfulness-based addiction treatment has consistent results for tobacco smoking treatment.

In context of stress, a self-perceived ability to handle stress without smoking at baseline predicted the subjects' abstinence at the 12-month follow-up (Nohlert et al., 2018). Stress management has its mainstay in non-pharmacological methods. Motivational and psycho-educational interventions are needed in smoking cessation treatment that aim at addressing the associated stress and anxiety (McHugh et al., 2017). Social support may be an important aspect to help individuals manage the stress experienced during early abstinence thereby improving prolonged cessation rates (Bandiera et al., 2016).

Figure 2. Overview in the management of tobacco addiction



## CONCLUSIONS AND FUTURE DIRECTIONS – ‘LOOKING FORWARD’

Tobacco use and psychosocial stress are intimately related mostly bidirectionally as shown by different animal models, clinical and epidemiological research. With the development of newer genetic, epigenetics, chemo-genetic and opto-genetics more

is probably going to be unraveled in the future about the underpinnings of ‘stress’ and ‘tobacco use’. This also unequivocally contradicts the much-touted belief that smoking relieves ‘stress’. There is currently good scientific evidence highlighting the moderators of the relationship between stress and tobacco use namely sex, emotional disposition and early life experiences. COVID-19, e-cigarettes and their interrelationship with stress and tobacco use needs to be researched in depth in the immediate future. In view of the importance of stress in the initiation, maintenance and relapse of tobacco use, stress management is an essential component of all tobacco cessation programs. Such programs need to be enriched with the application of third wave cognitive behavioural therapy (mindfulness, acceptance, meta-cognition-based approaches) and virtual reality approaches.

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## **STRESS AND TECHNOLOGY USAGE**

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### **OUTLINE**

- |                              |   |
|------------------------------|---|
| 1. INTRODUCTION              | 2. STRESS CAUSING PROBLEMATIC<br>TECHNOLOGY USE |
| 3. TECHNOLOGY CAUSING STRESS | 4. ASSESSMENT                                   |
| 5. MANAGEMENT                |   |

Stress is a common phenomenon that each one of us experience to some degree on everyday basis. Experiencing stress nowadays have become normal and, to some extent, a necessary part of life. Despite it being something, everyone experiences, what causes stress and how much it affects them can differ from person to person. The cause for stress is individual to each person, which means what can create pressure on someone can be seen as a challenge or opportunity by someone else. As an individual we are surrounded by numerous possibilities around us that can act as a catalyst for stress, be it physical, emotional or related to some factors present in the environment. Some of the main sources of stress for people can be related to their work, finances, personal relationships, parenting, and day-to-day hassles (Scott, 2020).

Another common element that people generally have to deal with in their day to day life is technology. In today's world, technology is increasingly integrated into every aspect of daily living from work to academics, banking, shopping, entertainment to socialization. Technology is transforming the society significantly and we seem to be dependent on technology for almost every facet in life. It makes

us possible to stay connected with others although we are distant apart, it allows us to fulfil several tasks without our physical presence, it brings up the information of whole world around us in just one click and is a major medium of entertainment for us. Other than what is mentioned above, technology provides us with numerous other advantages that cannot be counted on tips. It goes without any doubt that technology is making our lives easier, but at the same time it is challenging our present-day establishment, changing how we work, travel, entertain ourselves and even interact (Amos, 2016). Considering this aspect of everyday changing reality brought about by technology, there is a possibility that technology can be a source of stress for many people. This can hold true especially for people from the generations who are still struggling to get hold of this new revolution and are yet to come in terms with the various functionalities of it. Also, the changes brought about in our life by the technological advances can become difficult for some people to deal with. Technology is constantly evolving, so we feel responsible to be on track with the latest devices and software. We're continuously adapting our methods and skills, and that can lead to additional stress (Peterson, 2017). There are also indications in research that technology usage might be related to greater level of stress among people. A correlational analysis study to examine the relationship between technology and negative mood states found stress was positively predicted by technology use according to path analysis results (Akin & Iskender, 2011). Other research has also found that psychological factors such as stress are also present among individuals who are addicted to technology (Lodha 2018; Yen et al., 2010). Thus, the literature suggests there is a definite relationship between Stress and Technology use but the main question remains that how does the interaction play out.

According to Compensatory carry-over action model, different health related behaviors interact to facilitate higher level goals that is emotionally relevant to an individual which in most case is work-life balance and personal well-being (Lippke, 2014). Now problematic technology use may occupy the time one could spend on many health-related behaviours as physical activity, family time etc which can negatively affect the work-life balance (Gao et al., 2020).

There are studies indicating that technology use has a direct impact on stress as the problematic internet use was found to be related to perceived stress and negative feelings (Samaha and Hawi, 2016; Ostovar et al. 2016; Khalili-Mahani et al.,2019). Other studies have shown that perceived stress plays an important

role in problematic internet use (Li et al., 2016; Zhao et al., 2017). Hence, as per the *compensatory carry-over action model*, both perceived stress and problematic internet use may cause barrier between the relationship of health behaviours and a higher-level goal (ie, work-life balance) and affect the well-being of the person as a consequence. One of the important lessons to note from the several components of the model is that the association between Stress and Technology use is dyadic i.e. both the elements have been found to influence each other. Thus, in the upcoming sections we will discuss in detail what are the intermediate factors that plays a crucial role in the interaction between these two components of Technology & Stress. The following would be the outline of understanding how the relation between Stress and Technology unfolds: in the initial section we will look into how a) Stress can cause problematic technology use; in the next section we will discuss about the ways in which b) technology use can create stress and in the final section we will talk about c) strategies for management of stress related to technology use

## **STRESS CAUSING PROBLEMATIC TECHNOLOGY USE**

The following are the factors identified in the literature that appears to play a role in giving rise to excessive technology use due to stress:

### **Psychological Need Satisfaction**

Deci & Ryan (2000) explained this need in their self- determination theory according to which individuals have basic mental requirement for autonomy (i.e., the feeling of being self-determining in one's behaviors), relatedness (i.e., the feeling of closeness and connectedness to others), and competence (i.e., the feeling of dealing with issues in a competent way). These basic psychological needs are essential "nutriments" for well-being and personal growth for any individual. If people are unable to fulfil these psychological needs in one social domain for an extended amount of time, they might feel frustrated and becoming dysfunctional. As a result, they would be motivated to seek satisfaction for these needs in other social contexts. From this perspective, psychological needs are not only experiential outcomes that are affected by social factors, but also internal motives that brings about corrective actions when any experience is not appealing (Sheldon & Gunz, 2009; Sheldon et al., 2011). Hence as per this contention the psychological needs satisfaction is an instrumental motivational mechanism that explains how social environmental factors impacts human development. Hence, deducing from this theory, it has been proposed that the satisfaction of psychological needs may be an important factor that mediates the relationship between stressful life events and Problematic

Technology Use (Li et al., 2016). There are several researches that have found that severe stressful life events affect the psychological needs satisfaction (Raufelder et al., 2014; Ye et al., 2013). The researchers have concluded that as stressful life events increase, individuals' satisfaction of psychological needs decreases. Moreover, the satisfaction of psychological needs depends on the extent to which the external environments respond to the psychological demands. When due to stressors and unyielding socio-environmental factors, our psychological needs are unmet, it can prompt the use of technology to gratify those needs. According to the theory of Compensatory Internet Use, the stressful life situations can give rise to a motivation to use technology for alleviating negative feelings. The basic assumption of this theory is that problematic technology use is a reaction by the individual to his negative life situation, facilitated by the applications present over technology. For example, if a person in real life is not able to interact much socially, s/he reacts with a motivation to go online to socialize which is facilitated by an application where socializing is afforded, such as an online game or a social networking site. There can be both positive and negative effects associated with it. It can be positive in the sense that the individual feels better since he gets the expected social stimulation that gratifies his internal needs and negative because he may not go out and make new contacts in person (Kardefelt- Winther, 2014).

To summarize, individuals whose basic psychological needs are not met in real life are more likely to experience psychological distress, which in turn increases the possibility of addiction to technology and largely it is the stressful life events that negatively impact their psychological need satisfaction. Therefore, the stressors in life events can cause frustration of the psychological needs, which in turn can increase our dependence on technology by virtue of numerous features the latter possess. That is, psychological needs satisfaction will mediate the association between stressful life events and excessive technology use (Li et al., 2016).

### **Inadequate Coping Style**

Stress is usually associated with significant negative life changes such as setback in work or personal relationships. These changes also require us to adjust and adapt to them. Coping usually involves adjusting to or tolerating negative events or realities while attempting to maintain our emotional equilibrium. The way people respond to stress differs individually. Coping style refers to a person's general tendency or enduring disposition to handle stressors with a specific set of coping strategies (Lazarus & Folkman, 1984). There are two distinct coping styles

adopted by people in face of stressful situations: Positive or Approach oriented coping includes strategies such as problem-solving, support seeking, and cognitive restructuring that aim to directly address the stressors and Negative or Avoidant coping, in contrast, which includes strategies as denial, blaming, social withdrawal, and disengagement that aims to avoid the stressful situations (Zheng et al., 2012).

Almost everyone faces with stressful life events at some point of their life but not all of us have difficulty technology addiction as a result of these events. Thus, the outcome of excessive technology use must be an interaction of stressors as well as inherent individual characteristics that seems to exacerbate the impact of these events and making people prone to unhealthy habits such as technology overuse. According to stress-coping theory (Carver & Vargas, 2011; Lazarus & Folkman, 1984), a stressor generally doesn't negatively impact individuals who possess effective coping resources. Simply put, stress alone doesn't influence a person's overall well-being but how well the person copes with this stress determines whether the stress will be able to impact their functioning or not. If coping is ineffective, small amount of stress can be substantial and may have damaging socio-occupational consequences. However, if coping is effective, stress is likely to remain under control. Researchers have found support for this theory in several studies which show that coping style moderated the relationship between stressful life events and various pathological outcomes, including substance use, externalizing problems, and internalizing problems (Wills, 1986; Gonzales et al., 2001; Kraaij et al., 2003; Vera et al., 2011; Zheng et al., 2012). In similar line, some research has documented that negative coping especially avoidant coping plays an important role in Technology addiction (Li & Lei, 2005; Zhou, 2009).

Therefore, we understand that the direct and/or indirect associations between stressful life events and Overuse of technology via psychological needs satisfaction will vary as a function of individual coping style. The positive coping is known to enhance our response to the stressful life events and in contrast, negative coping can be a moderator between stressful life events and Technology via psychological needs satisfaction (Li et al., 2016).

### **Mood Modification**

Internet application these days are very interactive because of the various new features and upgrades in technology. Some of these features as online chat and multiplayer online games enables the creation of an online stimulation that are

extremely appealing and may change users' states or moods which include reduced loneliness, improved self-esteem, happiness and well-being (Young, 1998). There are studies that excessive Internet use brings about a positive mood-change effect derived from the online stimulation associated with it (Cheak et al., 2012). Chappell et al. (2006) in his phenomenological analysis of people addicted to video gaming discovered that online players become physiologically simulated while playing and they significantly mentioned about the exciting feeling of positive mood change experienced while playing computer games. Although the mood modification effect was a central finding for most of the participants, the researcher contends that this might have been influenced due to other factors like personality types or sensation-seeking traits. Therefore, compulsive use of technology provides a psychological escape mechanism to avoid real or perceived problems. This escapism leads a person to depart from an unpleasant reality in order to create a virtual "ideal self" liberated from real-life stress and limitations (Li et al., 2011). Hence, it appears that people use technology on a regular basis in order to change their negative mood or to escape from everyday life problems or stressors. Using the technology to alter mood by involving in online social interaction & networking or playing multi-player games might not always necessarily lead to negative consequences of excessive and compulsive use, and experiencing psychological withdrawal (Widyanto & Griffiths, 2006). However, such engagement can be also be seen as a coping strategy that makes them feel better and relieves the daily stress.

### **Illness Anxiety and Information-Seeking**

Stress and health related illness have a complex relationship, which is dyadic. Knowledge of having serious health problem can be a strenuous situation in one's life especially when the illness is chronic or terminal. The illness itself becomes a source of stress that the person requires to adapt with in their life. On the other hand, chronic stress also has a significant effect on the immune system that ultimately manifest as an illness or deteriorates the health condition. Illness or health anxiety are increasingly becoming common among people which is marked by excessive worry that one is or may become seriously ill. Having physical illness have also been significantly correlated as a form of stress leading to mental health problems as well (Rawson et al., 1994). Nowadays, technology, especially the internet holds an important place in the process of gathering information regarding health. Studies have found that more and more people are turning towards internet to seek health related information. According to one survey in U.S., around 90% of adult Internet users have looked for health-related information online on at least

on one occasion. Surveys held on a global level also holds that approximately 75% of participants make use of the Internet for health-related searches. The availability of health information on the Internet has many benefits (Bagaric & Jokic-Begic, 2019). The access of information available on the Internet serves many purposes as it makes the patients aware of different treatment choices at their disposal, expand more on the personal information received from medical staff about the illness and to find desired information anonymously and quickly. However, this practice can also be troublesome because of lack of authenticity of the information source and it can become a means of unhealthy expression for the anxiety triggered by stressful situation. The person with anxiety may repeatedly read up on information present online regarding their illness, that might lead them to negative and alarming information about their health and they might start believing to have symptoms that are not present in reality (Thakur P.C. et al., 2020). Hence, the stress associated with illness and health anxiety can foster a dependence over technology, that although initially could lead to some useful information and knowledge about health behaviours, but, it has also been found that extended and uncontrolled technology use regarding health information can itself be manifested as an unhealthy response to stress and cause greater mental health issue.

## **TECHNOLOGY CAUSING STRESS**

The following consequences that the technology usage can contribute to stress has been identified:

### **Physical Distress**

Along with the positive aspects of technology, it also presents many negative effects. One of the negatives technology consequences is the physical effect on the body. Excessive technology use can cause stress and strain in the body which is visible in the form of physical side effects such as tension headaches, eye strain, muscle pain, sleep and musculoskeletal problems. When you use a smartphone, the chances are that you're holding your head in an unnatural forward-leaning position. This position puts a lot of stress on your neck, shoulders, and spine. Overuse of technology can also lead to repetitive strain injuries of the fingers, thumbs, and wrists. Technology use also interferes with the sleep as a recent research suggests that exposure to the blue light that devices emit can suppress melatonin and interrupt your circadian clock that can make it harder to fall asleep and result in irritable mood and distress next morning. Having electronic devices in the bedroom places

temptation at your fingertips, and it can make switching off more difficult. That, in turn, can make it harder to drift off when you try to sleep.

### **'Constant Connectivity' Stress**

In recent times the profile of the “constant checker” is emerging due to excessive technology and social media use. The “constant checkers” are those who constantly check their emails, texts or social media accounts. This constant use of technology is associated with higher stress levels as reported by the users themselves. A 2017 survey done by American Psychological Association (APA) related to Stress and Technology Use, the findings around 18 percent Americans recognize the use of technology as a significant source of stress. Along with that around 86 percent of participants say they constantly or often check their emails, texts and social media accounts. The stress level was observed higher for constant checkers, than for those who do not engage with technology as frequently. Constant checkers reportedly admit as well that constantly checking devices is a stressful aspect of technology, compared to non-constant checkers. Political and cultural discussions on social media was identified as a major source of stress due to technology use among constant checkers. Furthermore, worry about negative effects of social media on physical and mental health was felt by 42 percent of constant checkers as compared to 27 percent of non-constant checkers. Constant checkers express feeling disconnected from their family, even when they are together, as a result of technology and report being less likely to meet with family and friends in person because of social media. Hence this survey highlights the frequent visiting and checking information online can become a point of stress and affect the person.

### **Social Pressure of Staying Updated**

Social media use in technology creates a platform for bragging; where possessions, events, and even happiness seems to be in competition at times. People are comparing their best, picture-perfect experiences, which may lead you to wonder what you are lacking. It has been noticed people who use social networking sites at a high rate may experience fear of missing out (FOMO) as a result. FOMO is a real phenomenon that is becoming increasingly common and can cause significant stress in your life. It can affect just about anyone, but some people are at greater risk. FOMO is not just the sense that there might be better things that you could be doing at this moment, but it is the feeling that you are missing out on something fundamentally important that others are experiencing right now. Social media sites like Instagram and Facebook has accelerated the FOMO phenomenon

in several ways. It provides a situation in which you are comparing your regular life to the *highlights* of others' lives. Therefore, your sense of "normal" becomes skewed and you seem to be doing worse than your peers. You might see you pictures of your close friend partying and having fun time without you that might make you feel miserable and dejected. As we found that social media use can induce the FOMO phenomenon, interestingly, on the other hand, FOMO acts as a mechanism that triggers higher social networking usage. A research study also found that adolescent girls & boys experiencing depression and anxiety tend to use social networking sites at a greater rate (Oberst et al., 2017). This shows that increased use of social media can lead to higher stress rates caused by FOMO. Aside from increased feelings of unhappiness and stress, FOMO can lead to greater involvement in unhealthy behaviours such eating disorders and body image issues.

### **Continuous Exposure to Negative Information, Online Aggression & Bullying**

Several incidences have been quoted and reports were given that online information and communication can have harmful effects and leave a strain on a person's psychological health. With respect to the negative communication prevalent in online world, a concept of 'Digital stress' has been coined, which is stress caused by negative interactions in emails, texts, social media, chat rooms and forums. It refers to the external demands of the digital world imposed on the digital users that affects their ability to cope adequately in terms of communication, multi-tasking, decreased productivity etc (Sharma et al., 2020). This stress can occur online due to hostility or personal attacks, through posting humiliating information on public platform and impersonating someone else and creating harm to the image.

It has also been reported that the social media use in digital technologies makes people more aware of stressful events in the lives of their close friends and family, as well as in the lives of more socially distant acquaintances, and that this in turn is related to higher levels of stress. Further, owing to the ease of fetching information over technology, we readily become aware of various negative events and information on our news feed all over the world that further lowers the mood and make us feel distressed. This phenomenon, of being affected by negative information around us, also known as **Cost of caring**, can take a heavy toll on our psychological health.

**Cyberbullying** is another misuse of digital technologies nowadays, mostly by youngsters and can be defined as aggression that is intentionally and repeatedly carried out in an electronic context (e.g., e-mail, blogs, instant messages, text messages) against a person who cannot easily defend him- or herself (Kowalski et al., 2014). This form of bullying is perceived as stress by the victim and can lead to various negative outcomes such as anxiety, depression, substance abuse, difficulty sleeping, increased physical symptoms, decreased performance in school or in extreme cases suicide (Ybarra et al., 2007).

### **Mental Exhaustion Due to Overuse**

When we are involved in a tiring activity for prolonged period of time, our body suffers from burnout which is a state of emotional, physical, and mental exhaustion caused by excessive and prolonged stress that makes one feel overwhelmed, emotionally drained, and unable to meet constant demands. The ICD-11 has moreover recognized it as an occupational phenomenon. Likewise, if we use the internet extensively, probability is high that we might feel burnout. **Digital burnout** is fatigue and stress caused by prolonged use of technology. It can be understood as hyper-connection to smartphones, laptops, and tablets which leaves us susceptible to burnout (Sharma et al., 2020). The technology makes it easier to transmit information than ever which might lead to overflow of information and result in cognitive overload. Due to the availability of vast content, sometimes people might feel that world of technology is the real world and there's nothing else we need to do other than that. In addition to cognitive overload, excessive technology time can make us feel deprived and unhappy, even if we are connected to many people online. Therefore, it is important that we become more conscious about how we use technology and don't keep aside our real life for it.

These days due to social restrictions mandate, people are working from home and connecting with their colleagues and friends over video conferencing. Zoom or another video conferencing platform for work, school, or social interaction as well causes increased time spent in front of a camera that is taking a toll on our physical and mental health. This brings us to another new concept of '**Zoom fatigue**', which resembles the emotional and physical strain that drains our energy levels. It is referring to the experience when our brain is overworked due to simultaneously processing only a few available visual cues (facial expressions vs. full-body) from several people at once in a way we never have to do in person. Hence, virtual meetings throw us in a stimulus-rich environment that muscles our brain to work

twice as hard. This taxing of brain is undoubtedly straining for the person who has to attend Zoom or virtual meetings and can be a major basis of stress.

### **Reduced Functioning, Affected Relationship and Disconnection from Real World**

Because of fatigue and unnecessary indulgence in technology, people are drifted away from what is going on around them. As discussed above, several social and entertainment features available in technology provides the users with several attractive options and they end up indulging major chunk of their time in them. As a result of this, they miss out on the real-life expectations of their job and personal relationships. The person might end up delaying the work required to be done urgently at the job or avoid going to work altogether. Family time and interaction with close friends are also affected as people might choose to spend more hours of the day with technology at the cost of ‘real-world’ social relationships. This can lead to conflict among them and they might end up remaining isolated. Overtime the person engrossed in the technology world don’t realise what is happening with them and when they actually identify the pattern, they notice themselves being in a great mess from which it is difficult to come out. Because of the excessive dependence on technology, people might end up having strained relationship with others and conflict with family members and poor work performance. This might cause them to feel depressed and make life more stressful.

## **ASSESSMENT**

The technology, as we know have become a salient requirement in today’s world for occupational, personal or social purposes. Hence, it becomes important to distinguish what extent of its use can be deemed as problematic / excessive. There are several screening instruments available that helps in evaluating the dependency over technology.

- **Internet Addiction Test (IAT)** [Young, 1998]

It is a 20-item scale, developed that measures the presence and severity of Internet dependency among adults. item scores are categorized as Normal Technology Use; Mild Addictive Use & Severe Addictive Use.

- **Internet Gaming Disorder Scale – Short-Form (IGDS9-SF)** [Pontes & Griffiths, 2015]

This scale assesses the severity of Internet Gaming and its detrimental effects by examining both online and/or offline gaming activities occurring over a

12-month period according to criteria defined by DSM-5. Higher scores indicate higher degree of gaming disorder.

- **Problematic Use of Mobile Phone (PUMP)** [Merlo et al., 2013]

This scale consists of 20 questions and the total scores ranged from 20-100. The higher scores indicate more usage of mobile phones and more problematic use.

Other than using Technology related screening tools, it is also recommended to check the stress level of the person to adequately assess the interaction of stress with technology use.

## **MANAGEMENT**

### **Stress Management**

Digital world can be extremely stressful especially with the enormous information flow and updates around us. Here are some useful tips to sort out the demands imposed by the digital world and have a healthy and productive digital use:

- Unsubscribe to information you one doesn't need to be exposed by unfollowing pages on Facebook, YouTube, and other social media accounts.
- Choose to opt out of social media tools such as Twitter/ Facebook that doesn't add value to life rather it makes you feel miserable.
- There are some apps over the phone that keeps buzzing and sending alerts creating an aura of false urgencies. It is suitable to turn off the notifications that aren't important and critical to be paid attention. This step would help us from losing distraction and keeping focus on the real-world task at hand.
- It is also a good idea to declutter the information on the digital sets and organize them as per the utility in a way that is easy to use.

Other than the features of technology creating pressure in our daily lives, our stress also becomes basis for excessive technology use as a function of tension-relief. It has been established that people often turn towards technology as a way of coping with their emotional problems. The lucrative features over the technology offers escapism from the real-world problems and the users prefer engaging more time in the online world. Hence, it is imperative that such people should imbibe

action- oriented coping style that assists them to deal with their life problem rather than running away from them.

### **Digital Detox**

A digital detox refers to a period of time when a person refrains from using technological devices such as smartphones, televisions, computers, tablets, and social media sites. “Detoxing” from digital devices is necessary as it provides a way to focus on real-life social interactions without distractions. It has been found that by letting go of digital devices, at least temporarily, people can let go of the stress that they have to face due to constant interference from the online world.

### **Balance Between Technology and Reality**

For many people, technology usage appears to overpower other daily life activities, which in turn can prove to be overwhelming for the person to handle. Hence, it is recommended to maintain a healthy balance between real and digital world. Technology has pervaded our lifestyle in every nuance and it appears that we have almost become a slave to them. Hence, it is important to get a life without internet/ technology at least for some part of the day where we can engage in real life activities and social interactions. This can be done by limiting our digital usage and set aside some time from our life for recreational activity without involving technology and pursuing some hobbies or engaging in physical exercise. It should be mandated in the family to have tech-free family time for at least one hour during dinner-time and/or family gatherings.

Usage of digital technology has its own issues in terms of blurred boundaries between work and personal life and reduced personal privacy. Although, it has greatly improved our lives as it's now far easier to connect with others and find information but time and again the demand of remaining connected to technology is extremely demanding and creating stress for the users. Whether we like it or not, digital technology is here to stay. The flood of information online won't change anytime soon and will likely worsen as more people avail its service. The way we can handle this pressure is to use digital tech in a conscious way, in a way that improves our lives rather than drains it. So, it is extremely important to figure out our boundaries and learn to use technology in a conscious way, in a way that aids us.

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## **STRESS AND PERSONALITY DISORDERS**

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### **OUTLINE**

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|---|---|
| 1. INTRODUCTION   | 2. STRESS AND PERSONALITY DISORDERS:          |
| 3. DIATHESIS STRESS MODEL                               | 4. PERSONALITY DISORDER AND STRESS GENERATION |
| 5. PERSONALITY TRAITS AND STRESS RESPONSE               | 6. STRESS AND BORDERLINE PERSONALITY DISORDER |
| 7. OTHER MENTAL HEALTH CONDITION & PERSONALITY DISORDER | 8. ASSESSMENTS                                |
| 9. INTERVENTIONS  | 10. CONCLUSIONS                               |

## **INTRODUCTION**

Stress is a non-specific response of the body to any demand for change. This chapter deals with the relationships between stress and personality disorders (PDs). Diathesis stress model and research evidences regarding developmental factors, personality disorder and stress generation, personality traits and stress response were discussed. This chapter also specifies how other mental health conditions other than stress influence personality disorder, assessment tools and treatment of persons with stress and personality disorders were analysed. The research evidences clearly support and revealed that there is a relationship between stress and personality disorders.

## STRESS AND PERSONALITY DISORDERS:

The prevalence of at least one personality disorder was 13.3%, with the majority (52.4%) presenting with obsessive-compulsive personality disorder. It reveals that a person with personality disorder were significantly more likely to be diagnosed with Post-traumatic stress disorder (PTSD) at 1-year follow up evaluation. This study concludes that pre-existing personality disorder may increase the risk of chronic PTSD (Malta et al, 2002).

Stress is an adaptation reaction of living organism in response to internal or external threats to homeostasis. Most of the previous studies have demonstrated that stress and personality are related. According to Williams et al, (2011) individual differences in personality influences stress exposure, reactivity, and recovery. Because altered stress processes are related to poor health outcomes (Reuben et al, 2016; Shields & Slavich, 2017), stressful life events and adverse life experiences represent potential mechanisms through which personality and its disorder may impact health (Gale et al, 2017; Iacovino et al, 2016; Smith et al, 2012; Timoney et al, 2017)

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Based on the complex relationships between stress and personality disorders, in which various forms of early life adversity, particularly experiences of abuse and neglect, portend the development of personality disorders and maladaptive personality traits later in life. Most of the literature suggests that acute stressful events later in development show complex interrelations with personality disorders. These connections appear to be bidirectional, such that not only does stress influence the development of personality, but personality also influences stress exposure. Additionally, personality traits influence the way in which individuals respond to stressors, both psychologically and physiologically (White et al., 2019).

On comparing the rates of traumatic exposure to specific types of trauma, age of first trauma onset, and rates of post-traumatic stress disorder, borderline personality disorder (BPD) patients reported the highest rate of traumatic exposure, the highest rate of post-traumatic stress disorder, and youngest age of first traumatic event. Those with more severe personality disorder (Schizotypal, BPD) reported more type of traumatic exposure and higher rate of being physically attacked (childhood and adult) when compared to other groups. These findings suggested that a specific

relationship between BPD and sexual trauma (childhood and adult) that does not exist among other personality disorders. This finding supported an association between severity of personality disorder and severity of traumatic exposure, as indicated by earlier trauma onset, trauma of an assaultive and personal nature, and more types of traumatic events (Yen et al, 2002).

Researches suggested that genetics, childhood trauma, verbal abuse and other developmental factors contribute to the development of obsessive-compulsive, narcissistic, and other personality disorders.

## **DIATHESIS STRESS MODEL (INTERACTION WITH PERSONALITY DISORDER):**

The diathesis-stress model is analogous to the multidimensional interaction model of stress, anxiety, and coping in the area of personality (Endler, 2002). Diathesis refers to a constitutional predisposition (to psychopathology or certain personality traits) that, when interacting with an environmental stressor, may induce a disorder or non-pathological trait. The core of this model is that both diathesis and distress are essential for the development of pathological disorders.

According to Linehan's biosocial theory (1993), the combination of a biological vulnerability to emotion dysregulation and an invalidating environment leads to borderline personality disorder. There has been some empirical research on etiology of personality disorders. For example, Caseras, Torrubia, and Farre (2001) investigated Gray's (1982) Behavioural Inhibition System (BIS) theory to determine if this system represents a vulnerability factor for the Cluster C personality disorders. They found that patients with Cluster C personality disorders (e.g., obsessive-compulsive, avoidant, and dependent) showed a higher BIS functioning, compared with patients with other personality disorders (Clusters A and B) and also compared with patients without personality disorders. This suggests that higher BIS functioning could represent a vulnerability factor. However, it also could be that higher BIS functioning merely indicate the presence of a Cluster C disorder.

## **PERSONALITY DISORDER AND STRESS GENERATION:**

Stress generation effects Cluster B Personality Disorders (i.e., antisocial, BPD, histrionic, and narcissistic), such that these were prospectively related to elevated rates of interpersonal dependent stressors in young women (e.g., Daley et al., 1998;

Iacoviello et al., 2007; Ilardi et al., 1997). Stress generation research indicates that even subclinical symptoms of personality disorders can influence the generation of subsequent stressful life events.

## **PERSONALITY TRAITS AND STRESS RESPONSE:**

Personality trait reflect person's characteristics pattern of thoughts, feelings and behaviours. The traits are considered as normal, prominent aspects of personality. Personality disorders results when the personality traits become inflexible and maladaptive, and cause significant social or occupational impairment, or significant subjective distress.

Less openness was associated with lower cortisol responses to the challenge. Cortisol responses also corresponded to certain personality dimensions in a gender-specific manner. The blunted cortisol responses were associated with higher Neuroticism in women and with lower extraversion in men. These findings suggested that personality traits that have been traditionally associated with greater psychopathology were also associated with blunted hypothalamic pituitary adrenal (HPA) axis responses to stress. Similarly, Xin et al (2017) examined the relationship between personality traits and the response to acute psychological stress induced by a standardized laboratory stress induction procedure (the Trier Social Stress Test, TSST). The stress response was measured with a combination of cardiovascular reactivity, hypothalamic–pituitary–adrenal axis reactivity, and subjective affect (including positive affect, negative affect and subjective controllability). The Generalized Estimating Equations (GEE) approach was applied to account for the relationship between personality traits and stress responses. The results indicated that higher neuroticism predicted lower heart rate stress reactivity, lower cortisol stress response, more decline of positive affect and lower subjective controllability. Individuals higher in extraversion showed smaller cortisol activation to stress and less increase of negative affect. In addition, higher openness individuals were associated with lower cortisol stress response. These findings revealed that neuroticism, extraversion and openness are important variables associated with the stress response and different dimensions of personality trait are associated with different aspects of the stress response (Oswald et al, 2006).

Four traits of big five personalities were associations with acute stress responses rather than extraversion. For extraversion, few studies did not found the relationship between extraversion and acute stress reactivity (Bibbey et al., 2013; Williams et

al., 2009; Schneider, 2004), some studies reported that higher extraversion was associated with more resilient psychological response to stress, such as more positive subjective feeling and a higher sense of control (Penley & Tomaka, 2002); a few and inconsistent findings exist in predictive value of extraversion on physiological stress response, with two studies showing opposite results of the relationship between extraversion and cortisol stress response (Oswald et al, 2006; Wirtz et al, 2007) and one study showed that higher extraversion predicted blunted stress response (Jonassaint, 2009). For openness, previous studies results suggest that higher openness is associated with attenuated negative psychological responses to stress, such as lower perceived stress and a smaller increase in negative effect (Penley & Tomaka, 2002; Schneider, 2012). Some studies report that higher openness was associated with lower cardiovascular reactivity (Williams et al, 2009; Lu et al., 2016). Other studies suggested that higher openness was associated with higher cardiovascular stress responses (Bibbey et al., 2013) and increased cortisol stress response (Oswald et al, 2006). In relation to agreeableness, Bibbey et al (2013) suggested that participants who were less agreeable had smaller cardiovascular and cortisol stress responses, it is not replicated in other studies (Oswald et al, 2006; Wirtz, 2007; Gracia-Banda et al., 2011). For conscientiousness, it was found to have positive predictive value in cortisol stress response (Gracia-Banda et al, 2011), while the others did not find the significant relationship (Bibbey et al., 2013; Oswald et al., 2006; Wirtz, 2007).

## **STRESS AND BORDERLINE PERSONALITY DISORDER:**

Borderline personality disorder (BPD) is characterized by severe difficulties in interpersonal relationships and emotional functioning. Theories of BPD suggest that individuals with BPD have heightened emotional sensitivity, increased stress reactivity, and problems in making sense of intentions of others. Based on the theories and assumption about borderline personality disorder, those who suffer from BPD have a lower tolerance to stress, have elevated reactions to stress, and have a longer recovery times from stressful events. Some studies found the strong relationship between stress and borderline personality disorder.

Stress increased subjective negative emotions in the BPD group to a larger extent than in the other groups, whereas physiological responses were decreased. Importantly stress induction increased negative evaluations about others, but to a similar extent in the BPD and CPD groups as in the non-patient control group. The study concluded that heightened psychological reactivity in BPD co-occurs with

reduced physiological responses to psychosocial stress and that stress affects social cognition to a similar extent in BPD as in others (Deckers et al, 2015).

Studies concerned with the influence of stressful childhood experiences and the development of personality disorders focussed largely on borderline personality disorder (Zanarini, 2000). BPD is typically a chronic mental disorder characterized by instability in identity, interpersonal relationships, and affective responses. Individuals diagnosed with BPD exhibit impulsive behaviours, often in the form of high-risk behaviours including self-injury, angry outbursts, substance abuse and suicidal behaviour. The person with BPD experience impaired functioning in various domains of life such as health and occupational functioning (American Psychiatric Association, 2013). BPD patient report significantly greater childhood adversity, particularly abuse (Soloff et al., 2002) and neglect (Johnson et al, 2000) than individuals with other PD's. Many researches suggesting that stressful life experiences in childhood may place an individual at a greater risk of developing BPD compared to other personality disorders. Borderline personality disorder had significantly higher rates of childhood or adolescent physical abuse (52.8% versus 34.3%) and were twice as likely to develop PTSD compared to subject without borderline personality disorder (Golier et al., 2003).

The relationship between coping strategies, personality disorders, and PTSD were explored using a treatment seeking sample of adult female survivors of childhood sexual abuse. A variety of personality disorders were found to exist in this population, with avoidant, antisocial, dependent PDs having higher frequencies than borderline PD. The finding suggested that the women with PTSD displayed higher rates of avoidant and dependent PDs, as well as more avoidant coping, than did women without PTSD (Johnson et al, 2004). More frequent deliberate self-harm among patients with (vs. without) PTSD and provided evidence for the moderating role of avoidant personality disorder in this association. Specifically, the results revealed heightened levels of DSH only among PTSD patients with co-occurring Avoidant Personality Disorder (Gratz & Tull, 2012).

## **OTHER MENTAL HEALTH CONDITION & PERSONALITY DISORDER:**

Personality disorders are a group of mental illnesses. It involves long-term pattern of thoughts and behaviours that are unhealthy and inflexible. People with personality disorders have trouble dealing with everyday stresses and problems. Apart from

stress, other mental health conditions also influences personality disorders. According to Parmar & Kaloya (2018), borderline and antisocial personality disorder are particularly found to be associated with substance use disorder and the prevalence of any personality disorder is higher among patients with drug use disorder than alcohol use disorder. The presence of depression may be a positive prognostic indicator for patients with borderline and antisocial personality disorder (Shea et al., 1992).

## **ASSESSMENTS:**

### **Assessment Tools for Personality:**

- 1. International Personality Disorder Examination (IPDE):** The IPDE was developed within the Joint Program for the Diagnosis and Classification of Mental Disorders of the World Health Organization (WHO) and U.S. IPDE screening questionnaire evaluates the presence of a personality disorder from 18 to 70 years and it features a 4th-grade reading level, self-administered format, and forced-choice response style. IPDE semi-structured interview assigns a definite, probable, or negative diagnosis for each personality disorder (Loranger, 1999).
- 2. Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD):** It is the updated version of the former structured clinical interview for DSM-IV Axis-II personality disorders (SCID-II). SCID-5-PD is a semi-structured diagnostic interview for clinicians and researchers to assess the 10 DSM-Personality Disorders across clusters as well as other specified personality disorders. This interview can be used to make personality disorder diagnosis, either categorically or dimensionally. The SCID-5-PD includes interview and the handy self-report screening questionnaire for patients (DSM-5 Screening Personality Questionnaire). This serves as a brief, 20 minute self-report screening tool to reduce the time of the SCID-5-PD interview. The questionnaire consists of 106 questions and requires an eighth grade or higher reading level (as determined by the Flesch-Kincaid formula). It has been used to investigate patterns of Personality Disorders co-occurring with other mental disorders or medical conditions (First et al., 2016).

### **Assessment Tools for Stress:**

- 1. The Clinical Stress Questionnaire:** The CSQ is a self-report, Likert-type instrument developed by Pagana in 1989 (reference) to determine the stressors

and level of stress. The questionnaire has 4 sub dimensions such as threat, damage, fight and benefit emotions.

2. **Depression Anxiety Stress Scale:** Depression Anxiety Stress Scale was developed by Lovibond & Lovibond, 1995. DASS-21 consists of 21 statements with four responses. The self-report instrument designed to measure the three related emotional states such as depression, anxiety and stress.
3. **Perceived Stress Scale:** The PSS, created by Sheldon Cohen. It is the most widely used psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful (Cohen, 1983).
4. **Ardell Wellness Stress Test:** Don Ardell developed this test assessment that is unique in its holistic approach to stress. The Ardell Wellness Stress Test incorporates physical, mental, emotional, spiritual, and social aspects of health for a balanced assessment.

## **INTERVENTIONS TO HELP PATIENTS WITH STRESS AND PERSONALITY DISORDERS:**

**Psycho-education (PE):** is defined as an intervention with systematic, structured, and didactic knowledge transfer for an illness and its treatment, integrating emotional and motivational aspects to enable patients to cope with the illness and to improve its treatment adherence and efficacy. This is specifically offer for individuals who are suffering from one of several distinct mental health.

**Cognitive Behavioural Therapy (CBT):** CBT is a highly effective, evidence-based therapy. Therapists have successfully used CBT to treat a variety of mental disorders particularly depressive disorders and anxiety disorders such as Obsessive Compulsive Disorder, and Posttraumatic Stress Disorder. CBT for personality disorder emphasis is placed on core beliefs that reflect the deep schema structures rather than on automatic thoughts that occur as a stream of thoughts in response to everyday situations.

**Acceptance and Commitment Therapy (ACT):** is an action oriented approach to psychotherapy that stems from cognitive behaviour therapy. It was initially developed by Steven. C. Hayes in 1982 for creating a mixed approach, which

integrates both cognitive and behavioural therapy. Rather than eliminating the difficult feelings of an individual, ACT helps a person to be with present and move towards a valued behaviour. ACT mainly focuses on 3 areas such as accept the reactions and be present, choose a valued direction and take action. ACT helps to treat workplace stress, anxiety, obsessive compulsive disorder, and psychosis. According to Morto et al, ACT treatment is valuable for person with borderline personality disorder.

**Dialectical Behaviour Therapy:** The only empirically tested approach is a cognitively behavioural therapy developed by Linehan called dialectical behavioural therapy. DBT was designed for severe self-mutilating and suicidal patients with BPD and focuses on changing belief systems and teaching more adaptive coping techniques. BPD not only effective for DBT, but also in other psychiatric disorders, such as substance use disorders, mood disorders, posttraumatic stress disorder, and eating disorders. Traditional DBT is structured into 4 components, including skills training group, individual psychotherapy, telephone consultation, and therapist consultation team. These components work together to teach behavioural skills. The skills include mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance.

**Stress Inoculation Training:** Stress Inoculation Training (SIT) is a multifaceted type of cognitive-behavioural therapy designed to help individuals cope with stress. It was initially developed by psychologist Donald Meichenbaum in the 1980s and has been employed to mitigate the stress in a variety of situations. The essence of SIT is that by exposing people to increasing levels of perceived stress, they practice employing different coping skills and eventually develop increased tolerance or immunity to a particular stimulus.

**Other Stress Management Techniques** Some stress management techniques such as relaxation training, exercise, yoga, guided imagery, progressive muscular relaxation, and assertive communication helps the individual to manage stress.

## **CONCLUSIONS**

The chapter clearly describes the relationship between stress and personality disorders based on the research evidences. Most of the researches indicated that there was a strong correlation between stress and borderline personality disorder. So, the person with stress and personality disorder can be managed by using specific

interventions such as cognitive behavioural therapy, dialectical behaviour therapy, acceptance commitment therapy and other stress management techniques. Hence, all the mentioned research evidences clearly discovered that there is a relationship between stress and personality disorders.

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## **STRESS AND SUICIDE**

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### **OUTLINE**

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|---------------------------------------|--------------------------|
| 1. INTRODUCTION                       | 2. INTERNAL RISK FACTORS |
| 3. ENVIRONMENTAL FACTORS              | 4. THEORIES OF SUICIDE   |
| 5. NEUROBIOLOGY OF STRESS AND SUICIDE | 6. CONCLUSIONS           |

## **INTRODUCTION**

Evolutionary theory holds that the evolution selects the behaviours that help in existence and development of a species, and suicidal behaviour defies this basic principle of evolution (deCatanzaro, 1980). Suicide occurs because of complex interactions between biological and environmental factors. Suicide severely impacts the personal and family domains of the affected individual. Suicide is a public health problem which is increasing in severity over the past few decades. The number of people who have died because of suicide has increased by 32% between 1999 to 2010(Lozano et al., 2012). As per WHO estimates of 2012, around 8 lakh people die every year worldwide due to suicide, which translates to one death every 40 second and 106 completed suicides per 10 lakh population, and at least 10 times more attempt suicide (Fazel & Runeson, 2020). As per latest NCRB report 1.39 lakh people died by suicide in India in 2019, and unfortunately 67% of them were between the age of 18 and 45, which are most productive years of an individual (Rampal, 2020) .

Hans Selye gave the concept of “general adaptation syndrome”, which is widely accepted concept of stress. The above syndrome consists of three phases

– alarm, resistance and exhaustion. Alarm phase is when the organism realises presence of threat / stressor thereby leading to production of adrenaline. When the stress persists, the next phase, “resistance” appears, and the organism tries to cope up with the stress using either good coping mechanisms or poor coping mechanisms. If the stress is more than what the organism can cope with, then the exhaustion phase appears, which may push the animal for self-destruction mode.

Selye also classified “stress” as either “eustress” or “distress”. “Eustress” is supposed to enhance performance through training or challenging work and distress is supposed to cause illness and reduce the performance of the organism (Selye, 1950). Lazarus, in his transactional model of stress and coping conceptualised stress in a different way, emphasising on the cognitive aspects of how the change is perceived. This model considers stress as a process in continuum, where the organism / individual is engaged in adaptive processes to bring back the equilibrium and thereby reduce stress. There are two components in development of stress, one is the cognitive appraisal (primary appraisal) of the new even / new environment other is effort to resolve the change or cope with the change (secondary appraisal). Theory of Lazarus is more comprehensive, since it also takes into account the cognitive aspects in development of stress (Biggs et al., 2017).

To summarise, both emphasise that stress can be managed upto a threshold and becomes unmanageable beyond that when the individual breaks down and this can manifest in the form of suicidal attempts or suicidal behaviours. Even the latest legislation on mental health, Mental Health Care Act – 2017, Sec 115 acknowledges the role of stress in suicide attempt and has decriminalised the suicide attempts (Vadlamani & Gowda, 2019) and also casted an obligation on the government to provide care, treatment and rehabilitation of person who have attempted suicide to decrease the risk and recurrence of suicide.

The point at which the stress becomes unmanageable and leads to breakdown in the individual depends upon two important factors a) internal environment (genetic vulnerability, coping skills, co-morbid medical conditions like diabetes, hypertension and past history of psychiatric illness) and b) external environment (quantum of stress, disaster, family support, social support, financial status and so forth). Multiple risk factors as listed above have been identified in the literature which can lead to completed suicide. These risk factors can be best understood using the life – cycle perspective, which states that in an individual who attempt

suicide, risk factors accumulate over his life time resulting in the final outcome of suicide.(Gunnell & Lewis, 2005). These factors can be either at the individual level or at the environment level, all of which lead on to increase in stress levels in an individual, so stress is considered as final common pathway in most of the suicide theories(Liu & Miller, 2014; O'Connor & Nock, 2014).

Even though in majority of the suicide, attempted suicide related behaviour, stress plays a major role, there are certain exceptions which cannot be explained by stress, like suicide by hunger strike, religious ending of life (santhara), altruistic suicides and suicide in terrorist attacks. We are not discussing the above mode of suicides. We are also not discussing about deliberate self-harm attempts, which are beyond the scope of this chapter.

## **INTERNAL RISK FACTORS**

Genetic factors are one of the most important internal risk factors for suicide. Both adoption and twin studies have reported higher chances of suicide attempt if there is family history of suicide (Brent & Melhem, 2008), but the research is yet to identify the specific genes associated with suicidal behaviour. Rate of suicide is different in different age groups. The overall trend in the world is that the suicide rates gradually increase with age and reach highest at more than 70 years of age. But this is not true in every country. Some countries have shown decreasing trend over the years and some have shown no correlation with age. (Shah, 2012). Suicide attempts are more common in women but completed suicides are 2 times more common in men. The above difference is known as gender paradox of suicidal behaviour. This paradox has been widely investigated and the reasons that have been unearthed are: men use more lethal means of committing suicide, men are more likely to face psychosocial risk factors of unemployment and retirement (Freeman et al., 2017)

Childhood adversity is a negative childhood experience which can affect the overall physical and mental health of the individual. Early childhood adversity can be in the form of childhood abuse, neglect, growing up in a dysfunctional household, parental separation or divorce, death in the family, parental psychopathology, substance abuse and criminality in the home, childhood poverty and residential instability (Björkenstam et al., 2017). All the above adversity factors are actually interconnected in a way, like for example parental psychopathology is likely to increase the financial instability, financial instability is likely to increase residential

instability and so on. The above-mentioned childhood adversity can result in disturbances in emotional stability and behavioural self-regulation resulting in impulsive and destructive reactions to any stressful events in future, thereby increasing the chances of suicide attempts(McGirr et al., 2008). Early childhood adversity is likely to result in poor academic achievement and this itself can also predict higher suicide rates in adults who were academically poor in their childhood. It is interesting to note that lower intelligence is not associated with increased risk of suicide, but only poor academic performance is associated with it (Kosik et al., 2017).

Among all the personality disorders Borderline and Narcissistic personality disorders are consistently associated with suicidal behaviour, because of presence of emotional dysregulation and impulsive aggression.(Ansell et al., 2015). Among psychiatric disorders depression, bipolar disorder, schizophrenia spectrum disorder and substance use disorder increase the risk of suicide by at least 10 times when compared to general population (Chesney et al., 2014). Physical Illnesses and terminal illness are another risk factor for suicidal behaviour. A recent systematic review found that functional disability and certain physical illnesses like malignant disorders, arthritis/arthrosis, liver diseases, neurological illnesses, male genital disorders and COPD are consistently associated with suicidal ideas.(Fässberg et al., 2016). Many patients with physical illnesses suffer from reactive depression, feeling of burden to others, loss of independence and other psychosocial issues which lead to development of suicidal ideas.

## **ENVIRONMENTAL FACTORS**

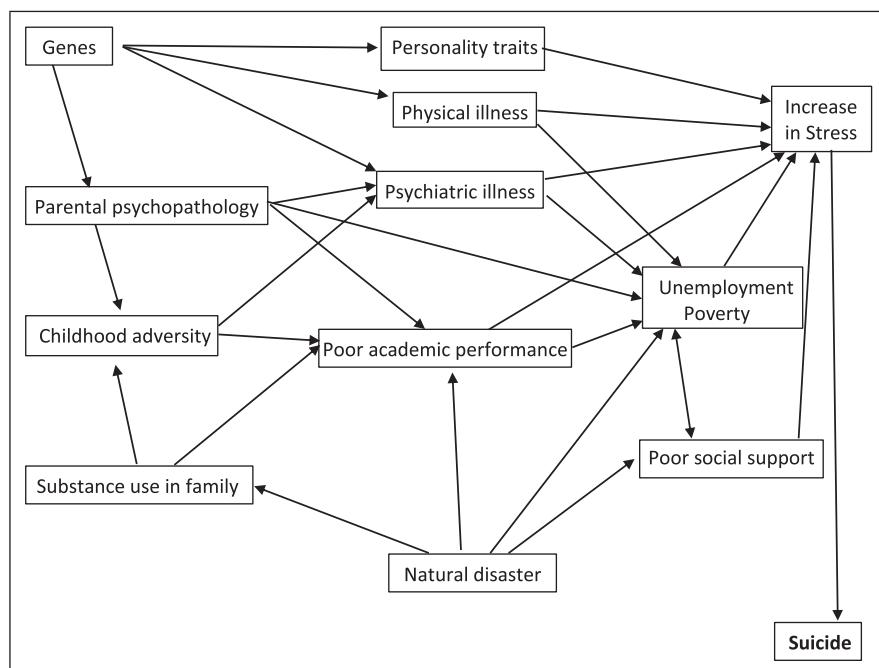
Multiple environmental factors increase stress levels of an individual and lead to increase in suicide attempts. Classically it had been described that being single is a risk factor for suicide among females, but recent literature suggests that suicide rates not significantly higher among singles. Poor social support and social integration are more predictive of suicide than marital status (Vijayakumar, 2015). In general, marriage appears to protect males (more than females) against suicide. Economic crisis has always been associated with increase in suicides because of unemployment and poverty (Uutela, 2010). A study done in brazil showed that the inequality of income between the individuals also increases suicide rates secondary to feeling of deprivation, persistent economic stress and feeling of helplessness(Machado et al., 2015). Rapid urbanization is another factor which can indirectly result in reduced social ties and increased stress levels creation of “fringe

population” who mostly live from hand to mouth and suffer from poverty(Trivedi et al., 2008)

Natural disasters, which are either natural or manmade, like earthquake, floods, famine, epidemics drought, terrorist attack, bombings, war etc are another set of environmental factors which severely impacts the individual’s mental health. Disasters, by definition is beyond the capacity of the community to cope and necessitates assistance from external world. So, the individuals of the community will face significant threat to their own life and life of loved ones, threat to food supplies, income source, shelter etc. All these increase the stress levels of the affected individuals, thereby increasing the chances of suicide(Krug et al., 1998).

The different risk factors that are discussed above actually interact with each other in complex manner, which we have tried to picturise in figure 1 as “web of suicide”.

**Figure 1: Web of suicide risk factors**



## THEORIES OF SUICIDE

Over the last 35 years or so significant research has been done in the area of suicide, there have been many models that have been proposed to understand suicide behaviour. In the below paragraphs we have discussed the theories that incorporate stress as a main factor in causation of suicide.

### **Shneidman Cubic Model of Suicide**

As per Shneidman suicide results from interplay of three factors, those are stress, psychache (psychological pain) and perturbation(O'Connor & Nock, 2014). Psychache is central concept in Shneidman model, which is nothing but intense unbearable psychological pain resulting from unfulfilled psychological needs. Psychological needs which are essential for life are love, belongingness, sense of control, positive image of oneself, and meaningful relationships. When the individual faces failure, rejection in life he/she is likely to experience psychache and he / she tries to find the solution to find relief from psychache but the individuals who fail to find relief from this pain might endup attempting suicide. .

### **Interpersonal Theory of Suicide**

As per this theory presence of two interpersonal characteristics are important in the development of suicidal ideations, those are “thwarted belongingness” and “perceived burdensomeness”(Joiner, 2009). Thwarted belongingness is the feeling that one does not belong to his/her family, friends circle or other valued groups there by experiencing a being alienated from others. The association between absence of belongingness and suicidal ideas has been well document in diverse population groups. Perceived burdensomeness is the feeling that one is a burden to his/her family, friends, or other valued group. Studies on the suicide notes have shown that those who had expressed opinion of being burden to their family / friends had more chances of completed and violent suicides(Joiner et al., 2002).

The presence of above two factors lead to development of passive suicidal ideations, but when the above two factors are perceived as constant and the person loses hopes of changing the above two opinions, he/she develops active suicidal ideations. But again, this itself is not sufficient for attempting suicide and requires presence of a third characteristic called “acquired ability for lethal self-injury”. This ability for lethal self-injury is not present at birth but is acquired later in life though life experiences. This develops gradually after repeatedly getting exposed to painful life experience, thereby resulting in habituation and higher pain tolerance finally leading to reduced fear to face the death (Joiner, 2009). Such painful life

experiences can be childhood trauma, being a witness to traumatic event, suffering from chronic sever illness, past suicidal attempts, etc.

### **Durkheim Theory**

As per Durkheim, suicidal ideations appear due to poor social integration and moral regulation of the individual. This model describes social causes for suicide. Even though this theory doesn't explicitly speak about stress, poor social integration which can lead to isolation, may act as external risk factor which effects the cognition of the individual leading to excessive feeling of loneliness and poor social support. So, isolation, loneliness and poor social support together act to lead to poor coping and increased stress levels thereby leading to suicidal ideations(Maimon et al., 2010).

### **Suicide as Escape From Self**

This model was proposed by Baumeister, which states that the chain of events are ignited following failure to meet ones standards and expectations. This failure leads to awareness of inadequacies in oneself thereby generation of negative affect which pushes the individual to escape from this self-awareness and attempt to end his own life.(Baumeister, 1990)

### **Stress Diathesis Models of Suicide**

There are multiple models that have been proposed on the basic principle of stress diathesis, as per these models when the individual is under severe form of stress he/she breaks down and engages in suicidal behaviours, but interestingly not all the individuals who are under severe stress engage in suicidal behaviour, this is determined by the presence of next factor "diathesis", which is nothing but vulnerability (van Heeringen, 2012) Stress can be in the form of psychosocial adversity or a psychiatric morbidity, infact there are significant interconnections between the two(Mann, 2003). The vulnerability develops due to multiple factors like genetic effect, childhood abuse, epigenetic mechanisms, personality traits, cognitive rigidity etc. it has also been suggested that the diathesis is actually a dynamic condition, which keeps increasing with repeated stressors in life, because of which we see the suicidal attempts of increasing severity over a period of time.

### **Arrested Flight Model or Cry of Pain Model**

This model, proposed by Williams and colleagues, goes beyond Baumeister's model of "escape from self" and draws parallels from the concept of "arrested

flight” from the animal behaviour research. Arrested flight is a condition where an animal is defeated, feels entrapped and the motivation to flight (escape) is blocked. A similar reaction is seen in humans which can precipitate depression and suicidal behaviour can be seen as a wish to escape from an unbearable stressful situation. Three components are very essential in this model, those are the presence of defeat, perception of no escape and perception of no rescue, leading to individual feeling powerless and hopeless and gets suicidal ideas(Rasmussen et al., 2010).

### **Cognitive Stress Diathesis Model of Suicide**

This model was proposed by Wenzel and Beck. The basic premises in this model is presence of three components, those are dispositional vulnerability factors, cognitive processes associated with psychiatric disturbance, and cognitive processes associated with suicidal acts Dispositional vulnerability factors can be personality factors, problem solving deficits, trait like maladaptive cognitive styles and impulsivity and related constructs. These factors are not considered risk factors by themselves, but they increase the likelihood that a suicidal crisis will emerge. Cognitive processes associated with psychiatric illnesses are nothing but cognitive schemas, which are cognitive structures that help us organise and make sense of the external stimuli. These cognitive schemas generally remain dormant until they are activated in stressful situations, after which they stimulate negative cognitive content and lead to biased information processing. Following this the cognitive processes that are associated with suicidal acts gets activated, which is hopelessness and this leads to development of suicidal ideas. (Wenzel & Beck, 2008)

### **Differential Activation Theory of Suicidality**

This was proposed by Teasdale. As per this model repeated stressful life events trigger negative cognitive schemas easily, similar to kindling that is seen in seizure disorder and bipolar disorder. So, this makes the person vulnerable to develop suicidal ideas to even minor stressful events over a period of time. In this theory also “stress” plays a very important role in causation of suicidal ideas(Lau et al., 2004)

### **Clinical Stress Diathesis Model of Suicide**

This model was proposed by Mann et all in 1999, based upon a clinical study they conducted on patients from psychiatric hospital. They found out that the people who attempted suicide, in addition to having higher scores of depression, they showed higher rates of borderline personality traits, outward aggression,

inward aggression, substance used disorders, head injury, impulsivity etc. In this model depression is considered as “stress” and rest of the factors are considered as “diathesis”, thereby increasing the risk of suicide(Mann et al., 1999).

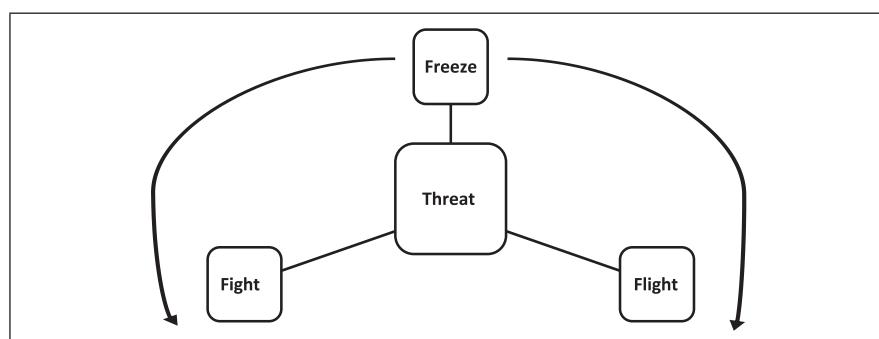
### **Integrated Motivational–Volitional Model of Suicidal Behaviour**

This model, proposed by O’Connor et al, is again based on stress diathesis model. There are three important components in this mode which are pre-motivational phase, motivational phase and volitional phase. Pre-motivational phase is the first phase consisting of triad of diathesis – environment – life events. Diathesis can be in the form of biological, genetic or cognitive vulnerabilities, environmental factors and life events can be in the form of early life adversities, parental psychopathology etc. All of these factors act in the background and increase the risk of suicide. Following this, in motivational phase, the suicidal ideations emerge, because of exposure to stressful event, leading to feeling of defeat, entrapment and hopelessness. Next is the volitional phase which is characterised by presence of volitional moderators, which convert the ideation to suicidal plan and suicidal act. The volitional moderators can be in the form of access to lethal weapons, witnessing suicide of family or friends etc(O’Connor & Kirtley, 2018).

### **Fight-Flight -Freeze Response to Stress and Its Relation to Suicidal Behaviour**

When an animal/individual encounters threat/stress, the body response can vary from fight that is counter the stress, flight to escape the situation or freeze wherein the body goes into state of collective immobility to enable the body to process and assess the threat and then reacting accordingly either fight or flight depicted in figure 2. This involves responses of different systems as below:

Fig 2: Persisting freeze reaction



When an individual has encountered repeated stress, like childhood adversity or experiences repeated severe trauma (such as victim of war, sexual or physical assault). The fight-flight-freeze responses are impaired. It has been seen that individuals who have experienced one or adverse events have prolonged freeze response when unpleasant pictures are shown to them, it was seen that the responses such as bradycardia seen in freeze response was more pronounced in those who had experienced trauma(Hagenaars et al., 2012). A recent study on physiological responses of suicide attempters showed diminished response when exposed to unpleasant simulated situations. It was noted that suicide attempters showed impaired introspection and diminished physiological responses and psychological responses in form reduced pain perception. The blunted responses is likely to increase harmful self-destructive behaviour(DeVille et al., 2020). Exaggerated freeze response indicated impaired problem solving, inability to cope which is likely to culminate in suicidal behaviour in at risk individuals who have high loading of the internal(Schipper et al., 2019) and external risk factor of suicide.

We can see that in all the above models stress is an especially important factor which can be conceptualised as a single common pathway leading to increased risk of suicide In the subsequent paragraphs we will discuss the neurobiological changes that follow stress there by leading to increase in suicide attempt and behaviours..

## **NEUROBIOLOGY OF STRESS AND SUICIDE**

### **Neurotransmitter and Neuroendocrine Systems**

#### **Serotonergic system**

Gene polymorphisms in serotonergic system and other neurotransmitters have been implicated in increasing the vulnerability of an individual to suicide. Relationship between depression and serotonergic system has been widely studied. In addition to being one of the causative factors for depression, serotonin system has been identified to moderate the influence of environmental stressors in depression. The serotonin transporter (5-HTT) is located on presynaptic serotonin neurons and its protein, which is responsible for the reuptake of serotonin, is encoded by single gene on chromosome 17. The “S” allele of the promoter region of serotonin transporter gene (5 HTTLPR) has lower transcriptional ability compared to its longer counterpart the “L” allele. The presence of one or two short allele “S” in promoter region of the 5HTT gene has been implicated in impaired ability to respond to stressful situations, thereby increasing the risk of depression and suicide behaviour in response to stress(Caspi et al., 2003; Currier & Mann, 2008).

It has been shown that early life stressors such as parental neglect, childhood physical and sexual abuse have influence on 5HTTLPR gene expression. When such individuals face stressor later in life, they will not be able to cope up and show increased incidence of impulsivity, violence and depression which independently further increase the risk of suicidal behaviour (Steinberg & Mann, 2020). Initial post-mortem studies on those with completed suicide and a diagnosable psychiatric disorder such as depression, schizophrenia, personality disorder, showed low levels of 5-hydroxyindoleacetic acid (5HIAA) in the CSF, this finding indicates a possible deficiency of serotonin. In contrast there is increase level of serotonin metabolites in the brainstem of individuals who have died by suicide (Bach et al., 2014). This contradicting finding is possibly due to compensatory increase in tryptophan hydroxylase proteins(TPH 2), more serotonin neurons with less serotonin transporter binding. It has been noted that in response to adversity, in childhood or in adulthood, there is an upregulation of 5HT1A transporter and increased binding in an attempt to compensate for the deficiency of serotonin. Altered genes as discussed above along with added adverse events cause impairment of serotonin function and impaired response to stressful events and thus making individual vulnerable to suicide or suicide behaviour (Menon & Kattimani, 2015).

### **Hypothalamic Pituitary Adrenal Axis (HPA)**

As seen with 5HTTLPR gene expression impacted by early life stressors, HPA axis genes are also influenced by the stressful life events which goes onto have long term consequences on individual's reaction to stress later in life. HPA axis dysfunction in response to stress is characterised by dysregulation of the hypothalamic peptides such as Corticotropin Releasing Hormone (CRH) and Arginine Vasopressin (AV) leading to excess of Adreno Cortico Trophic Hormone (ACTH) and Cortisol. Studies in individuals with suicidal attempts found single nucleotide polymorphism (SNP) of CRHR1 and CRHR2 gene following exposure to early childhood adversity. (Breen et al., 2015; Sanabrais-Jiménez et al., 2019).

Cortisol response to stress is necessary for coping with stress, however altered activity can have detrimental effects. Post-mortem studies of suicide victims have shown elevated levels of CRH in the CSF, indicating increased activity of the hypothalamic pituitary-adrenal (HPA) axis. Altered cortisol activity in response to stress, which can be either hyperactivity (acute stress) or hypoactivity (chronic stress), can increase the risk of suicidal ideations and behaviour (Eisenlohr-Moul et

al., 2018; Melhem et al., 2016). HPA dysfunction in reaction to stress is also linked with disturbances in serotonergic system and together can increase propensity for suicide behaviour in reaction to stress.

HPA hyperactivity has also been linked to personality traits of impulsivity, aggression, borderline personality disorder and in individuals with history of childhood adversity. Stress related HPA axis dysfunction also impacts cognition in the form of impaired learning and decision making. Individuals with history of exposure to childhood stress or chronic stress in adulthood are noted to have the impact on cognition as above, thus affecting the coping ability in stressful situations. Such individuals show increased risk of depression and suicide behaviours.

### **Noradrenergic system**

Norepinephrine (NE) system, primarily located in the locus coeruleus of the brain, is involved in stress response and occurs parallelly with HPA axis response to stress. Activation of NE in response to stress leads to vigilance, anxiety and enhanced arousal. There are two types of NE receptors,  $\alpha$ 2a which is stress promoting and  $\alpha$ 2b which is stress protective. CRF and NE interact with each other, CRF increases firing of Locus coeruleus and in turn increasing the release of NE in response to stress. Maladaptation of the CRF- NE circuits has been implicated in development of depression. Animal studies have demonstrated downregulation of noradrenergic system response to stress in the presence of early life adversity (Swinny et al., 2010). It has been seen that chronic stress leads to decrease in NE release in response to stress thus increasing propensity to suicide(Oquendo et al., 2014)

### **Dopaminergic system**

Dopaminergic system is known to be affected in individuals with depression, schizophrenia and alcohol use disorders. In terms of suicidality however no direct correlation has been identified. Dopamine Concentrations are noted to be increased in individuals with traits such as impulsivity and aggression, these traits are known factors which precipitate suicidal behaviour (Carballo et al., 2008).

Serotonergic system, HPA axis, Noradrenergic system interact with each other in adaption to stress – acute or chronic. When the compensatory mechanisms to combat the effect of stress fails it increases the risk of suicide behaviour in an individual when exposed to stressful situation.

### **Epigenetics, Stress and Suicide**

Epigenetics refers to a heritable but mutable set of processes that regulate the expression of particular genes in certain cell types and/or at specific developmental time points (Autry & Monteggia, 2009). Epigenetic mechanisms are influenced by both internal and external environments of an organisms. Epigenetics process begins right after conception (in the womb during pregnancy), during the lifespan of the individual and finally can be passed on to the progeny and their progeny (Lacal & Ventura, 2018). Epigenetics involves modifications in DNA methylation, transcriptional process of the Ribonucleic acid (RNA) and histone modifications. Early life experience and environment have shown to influence DNA methylation of HPA response to stress. Animal studies have shown that maternal warmth and affection towards new born rats and new born pups has effect on the methylation of the DNA and impacting the expression of glucocorticoid receptors (GR) genes and thereby affecting the organisms stress response later in life. It has been seen that the pups with less maternal warmth showed hypermethylation of GR genes, which later on impaired coping with stressor (Gould et al., 2017; Meaney & Szyf, 2005).

Epigenetic mechanisms demonstrate the effect of early life adversities, influence of external environment and its interactions with the DNA methylation process increasing the risk of psychiatric illness such as depression, schizophrenia, substance use disorders. Psychiatric illness such as depression has shown hypermethylation of GR genes and influence the 5HTTLR genes thereby independently increasing the risk of suicide and suicide behaviours through epigenetic mechanisms. Epigenetic mechanisms have been also been able to explain the role of Brain derived Neurotropic factor (BDNF) genes methylation in development of depression and in turn increase the risk of suicide (Jokinen et al., 2018; Mann & Currier, 2010).

### **Transgenerational epigenetic influences**

Epigenetic mechanisms and changes in DNA methylations or RNA transcription is not limited to the affected individual. It has been seen in children of parents who had been exposed to major stressors and these children are at increased risk of developing psychiatric illness such as depression, anxiety disorders, substance use disorders(Yeshurun & Hannan, 2019). Transgenerational transfer of the epigenetic factors is through the maternal germline and paternal mitochondrial RNA(miRNA)(Babenko et al., 2015). Transgenerational transfer of the epigenetic and the vulnerability to various psychological factors can get transferred from one

generation to the other (intergenerational transfer of the epigenetic changes). This is important to understand in order to identify vulnerable individuals early and provide early intervention to prevent long-term consequences of stress/suicide.

### **Hercules model of stress and suicide**

When someone hears the name Hercules, first thing that strikes their mind is endurance, physical strength, victory and one with extraordinary powers, thus it might appear paradoxical when we propose the “Hercules model of stress and suicide”.

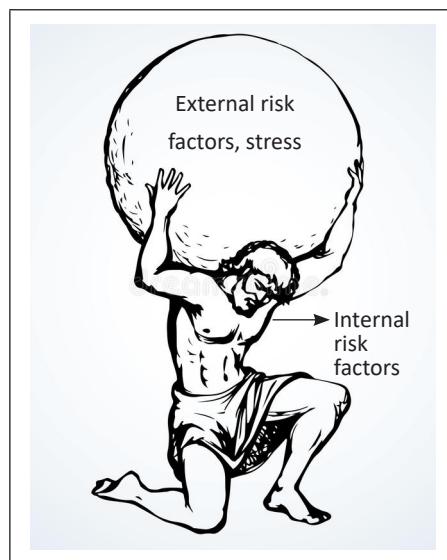
Hercules, the mythological Greek demi-god had faced multiple hardships right from his birth, faced with challenges throughout his early life; he has been described to be the one who never gave up when he faced with difficulties. He fought battles for others and won many and also fought battles for his own freedom and right. Being a victim of wrath of Hera, Goddess who was Zeus Wife (Zeus was Hercules biological father), and endless barriers set by her, he fought them and won. Having lost his dear ones (wife and children) by his own “insanity”, again which was deed of Hera, he took up and completed “12 labours” given to him, to cleanse himself from the sins of killing his family. Hercules death was a consequence of his enmity from the past which caught up with him. In the end his wife killed herself for causing suffering to her husband which would eventually lead to his death. Knowing his death was coming soon and having overcome with immense physical pain due to the poison; which would lead to slow death, Hercules is said to have built his own Funeral pyre in the end.

Life of Hercules had been far from easy and simple. Like life of many of the vulnerable individuals, life of Hercules was always filled with difficult situations throughout and he appears to have faced them with positive stride. If we come to the discussion to the topic of stress and suicide, Hercules faced with abandonment and hardships from his childhood, dealing with the consequences his “insanity” which set him on course of tasks to deal with the guilt and emotional pain. He was faced with challenges which seemed endless and ultimately led to death of his mortal form. In the previous sections we have discussed about various vulnerable factors which predispose an individual to suicide and suicide behaviour. Akin to the life of Hercules, every individual hope to endure hardships, be successful and victorious when faced with stressors. On the exterior, others may view a person as being able to deal with any amount of “stress”. Some individuals however are unable to

take the “weight” of the burden i.e stressors due to the “internal risk factors” and “External risk factors” which may outweigh the strengths and culminate in suicide or suicide behaviour. Thus we describe the “Hercules model of stress and suicide” describing the interaction between the **internal factors** (Biology) and **external factors** (environment and interpersonal relationships), which either protects the individual or puts the individual at risk for suicide.

As seen in the figure 3, strong Hercules can be equated with the strong protective internal factors or absence of internal risk factors, the weight he is carrying can be equated to the external risk factors including stress. When the internal risk factors are minimal or absent, that is when the Hercules is strong, he can withstand higher amount of external risk factors (weight in the image) including stress. If there are multiple internal factors like genetic predisposition, physical illness or psychiatric illness, that is when the Hercules is weak, he is likely to collapse even with minimal external risk factors (weight in the image). This is a simplified concept to understand the interplay between different risk factors.

Figure 3: Hercules carrying weight



## CONCLUSIONS

To conclude, multiple risk factors (both internal and external or genetic and environmental) interact with each other and lead to increase in stress levels and suicide. Early Identification of the vulnerable factors and arresting cascading effects of the vulnerable factors which likely to result in suicide when faced with further stressors is vital step.

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## Part IV

# STRESS AND SPECIFIC POPULATION



*Part IV of the book focussed on the implication of stress in various special/specific populations. It ranges (gender and age-related) from the child, adolescent, women, and geriatric psychiatric disorders. Given the developmental disorders present more relevant in children, it is also covered in this part. The situation relevant stress chapters focus on disaster, and occupational stress are discussed about stress and its role. The role of stress among the caregiver of psychiatric patients are also covered in a chapter. Because various medicolegal issues of stress are arising these days, a dedicated chapter attempts to tease out the implication of stress from forensic psychiatry point of view.*

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## **STRESS AMONG WOMEN- CAUSES AND CONSEQUENCES**

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### **OUTLINE**

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|--|---|
| 1. THE GENDERED NATURE OF STRESS                         | 2. DIFFERENTIAL EXPOSURE AND<br>DIFFERENTIAL VULNERABILITY<br>AMONG WOMEN |
| 3. SOCIAL ROLES AND STRESS                               | 4. VULNERABILITIES AMONG WOMEN  |
| 5. THE ROLE OF WORK IN CAUSING OR<br>AMELIORATING STRESS | 6. THE NATURE OF STRESS IN DIFFERENT<br>LIFE STAGES IN WOMEN              |
| 7. MANIFESTATIONS OF STRESS IN<br>WOMEN                  | 8. CONCLUSIONS  |

### **THE GENDERED NATURE OF STRESS**

Stress may be defined as a real or interpreted threat to the physiological or psychological integrity of an individual that results in physiological and/or behavioural responses (McEwen, 2019). Brown and Harris (1978) in their influential social theory derived from research with socially disadvantaged women concluded that it was the coincidental experiences of entrapment and humiliation that led to despair, hopelessness, worry and depression. Entrapment and humiliation are inherent to poverty, violence and gender discrimination.

There is a considerable amount of evidence indicating that women are both more psychologically and physiologically reactive to stressors than men (Holzhauer et al., 2017; Ali et al., 2020). The aspects in which these have been noted includes

greater heart rate (Kudielka et al., 2004) (Labouvie-Vief et al., 2003) (Smith et al., 1997) (Stoney et al., 1987), greater emotional responses (i.e., use of emotion words) (Sells & Martin, 2001) and greater self-reported psychological responses (such as, stress, intrusive thoughts and avoidance) (Lepore et al., 2000).

Differences in how men and women respond to stressful events may be a key factor in explaining the gender differences in the risk for developing stress related complications. For example, some studies have shown that women report greater subjective distress than men in response to stressful life events (Matud, 2004), and exhibit greater physiological reactivity to laboratory challenge (Kudielka et al., 2004) (Labouvie-Vief et al., 2003).

Fundamental to the stress model of illness is susceptibility to psychological or physical breakdown that is shaped largely by inequalities in life chances emerging from the organization of gender, class, race, age and other social statuses (Gerhardt, 1989).

## **Differential Exposure and Differential Vulnerability Among Women**

In examining susceptibility to stress as a basis for gender differences in health, research focuses on two hypotheses: *differential exposure* and *differential vulnerability*. The *differential exposure* premise proposes that women report more ill health than men because of higher levels of demands and obligations in their social roles. By implication, equal allocation of social role conditions ought to eliminate gender differences in health. The *differential vulnerability* hypothesis talks about greater reactivity or responsiveness by women compared to men who experience in equal measure, to life events and ongoing strains. It discusses that gendered reactivity stems from a generalized female disadvantage in social roles and resources for coping influences the nature and meaning of stressors and, ultimately, harms health.

Studies consistently find gender differences in certain measures of health, such as anxiety, depression, and some physical illnesses (Husky et al., 2018; Picco et al., 2017; Mirowsky & Ross, 1995; Barnett et al., 1987; Cleary, 1987; Nolen-Hoeksema, 1987; Weissman, 1977). While the reason for this discrepancy is not clear, one of the contributing factors could be stress differences (Li & Graham,

2017; Assari & Lankarani, 2016; McDonough & Walters, 2001; Mirowsky & Ross, 1995; Turner et al., 1995; Baum & Grunberg, 1991; Aneshensel & Pearlin, 1987; Baruch et al., 1987)

Gender affects each element in the stress process, by determining whether a situation will be perceived as stressful during the initiation to impacting coping responses and the health implications of stress reactions in the outcome (Smith & Hatmaker, 2017; Karkoulian et al., 2016; DePasquale et al., 2015; Baruch et al., 1987). Even though the literature studying the relation between gender and stress reveals several contradictory results, several authors have determined that women find themselves in stressful circumstances more often than men (McDonough & Walters, 2001) (Almeida & Kessler, 1998). Other authors have proposed that it is possible that women appraise threatening events as more stressful than men do (Miller & Kirsch, 1987) (Ptacek et al., 1992). Furthermore, studies have found that women have more chronic stress than men (McDonough & Walters, 2001) (Nolen-Hoeksema et al., 1999) (Turner et al., 1995) and are exposed to greater daily stress related with their routine role functioning (Kessler & McLeod, 1984). Women are also more likely to report home and family life events as stressful (Oman & King, 2000) and stress related to gendered caring roles (Lee, Colditz et al., 2003) (Walters, 1993). In addition, women experience gender-specific stressors such as gender violence and sexist discrimination, which are associated with women's physical and psychiatric events (Heim, 2000) (Klonoff et al., 2000) (Koss, 1991) (Landrine et al., 1995). Women, by nature of being more emotionally involved than men in social and family networks, get more affected by the stress of those around them. (Turner et al., 1995) (Kessler & McLeod, 1984).

## SOCIAL ROLES AND STRESS

The most dominant theoretical orientation regarding gender and stress explains women's disadvantage in terms of role theory—e.g., dual role occupancy (work and family) or role overload (Barnett et al., 1987) (Gove & Tudor, 1973)—rather than prejudice and discrimination per se. The effect of social roles on mental health may depend on the number or the quality of the individual social roles. According to the role strain theory, performing multiple social roles can be a source of stress due to paucity of time and energy, and may have largely unfavourable mental and health outcomes (Aneshensel & Pearlin, 1987) (Aneshensel et al., 1981) (Cleary & Mechanic, 1983).

Role occupancy regulates the range of potentially stressful experiences, increases the chance of exposure to some stressors and precludes the presence of others. But as Aneshensel and Pearlin suggest, the conditions people face once they occupy a role will be a source of differential stress, since different people may have very different experiences within the same role. Women and men differ in the frequency of their occupancy of specific social roles and also in their experiences within similar social roles. Women's position at work and in the family is less favourable since they carry a greater burden of demands and limitations (Cortes & Pan, 2018; Matthews et al., 1998; Mirowsky & Ross, 1995).

## **VULNERABILITIES AMONG WOMEN**

Gender disadvantage among women includes several important aspects like poverty, discrimination, powerlessness and limited access to resources and restricted choices, in varied circumstances such as in the choice of marriage, decision making in the marriage or workplace issues; many of these factors coexist and compound the impact of the disadvantage. Several studies from around the world have indicated that each of these negatively impact mental health (Gibbs et al., 2018; Golin et al., 2017; Chandra & Satyanarayana, 2010).

In the context of understanding the nature of stress, it is important to distinguish between traumatic life events, more common stressful events, daily hassles and perceptions of stress and also to understand that sex differences in the experience of stress greatly depends on the nature of the trauma / stressor (Folkman, 2011). Past research on the mental health of women provides evidence that there exists a differential exposure and differential vulnerability to stressful events based on sex differences (Blanco et al., 2018; Rubinow & Schmidt, 2018; Nolen-Hoeksema & Keita, 2003). Differential exposure puts forward that women are more depressed than men because they experience a certain kind of stressful event to a greater extent. Contrastingly, differential vulnerability implies that certain stressful events are more strongly associated with distress among women than men. In contrast to men, women are more likely to experience chronic sources of strain such as discrimination, poverty, sexual harassment and care-giving for young children and older persons (Hackett et al., 2019; Folkman, 2011). We shall briefly discuss below regarding some of the major factors that are identified as contributing to stress among women.

## **Discrimination**

Gender-based discrimination is one of the key determinants of health outcomes among women. While women can experience discrimination as a result of many diverse characteristics, gender discrimination independently impacts women's mental and physical health over other non-gender specific stressors, like experiencing major life events and hassles of daily life (Riecher-Rössler, 2017; Klonoff et al., 2000). Perceived gender discrimination has been found to be significantly related to higher reports of stress, anxiety, depression and premenstrual symptoms (Andersson & Harnois, 2020; Kucharska, 2017; Klonoff et al., 2000; Landrine et al., 1995), as well as psychological distress (Moradi & Subich, 2002).

Perceived discrimination (i.e. workplace, gender, race/ethnicity, and sexual-orientation based), has been identified as being a primary factor in chronic stress-related health disparities among vulnerable populations (de Castro et al., 2008) (Williams & Mohammed, 2008) (Meyer et al., 2008) (Guyll et al., 2001).

Stress experienced due to discrimination can contribute to adverse birth outcomes, when combined with the effects of general & maternal stress (Nuru-Jeter et al., 2008) (Dominguez et al., 2008) (Canady et al., 2008) and plays a role in the development of unhealthy behaviours such as substance use, improper nutrition and refusal to seek medical services (Lee et al., 2009) (Peek et al., 2011).

## **Sexual harassment**

The consequences of sexual harassment among women are varied and serious. The effects of sexual harassment vary from person to person and are dependent on the duration and severity of the harassment they were subjected to. Thus, individuals can suffer through a number of psychological effects ranging from irritation and frustration to stress, anxiety, and fear. This may lead individuals to developing a fear of retaliation and victim blaming.

Majority of the women who experience sexual harassment suffer from some debilitating stress reaction, including anxiety, depression, frustration, weight loss or gain, headaches, nausea, sleep disorders, lowered self-esteem and sexual dysfunction. Survivors of sexual harassment can experience long-term depression, have feelings of self-doubt and for some this might also turn into guilt and self-blame. They may also exhibit withdrawal and isolation (Thurston et al., 2019;

Houle et al., 2011). There can be a tremendous fear of retaliation and backlash, both institutionally and to the community of one's specific discipline or career path. In addition to these, some of the potential effects a survivor may experience include retaliation from the harasser, or colleagues/friends of the harasser, having to drop courses, or change academic plans. It may impact grade performance, result in increased absenteeism to avoid harassment, or because of illness from the stress. Stress impacting relationships with significant others, sometimes resulting in the termination of the relationship and similarly might place a strain on peer relationships and relationships with colleagues.

### **Violence**

Several studies have been conducted on the physical and mental health consequences of partner violence among both clinical and non-clinical male and female populations from different parts of the world (Loxton et al., 2017; Delara, 2016; Soleimani et al., 2016; Coker et al., 2002). Even though there are chances for both men and women being victimized are present, women are more vulnerable to violence from an intimate partner than men. Violence against women is a known cause of stress and is strongly correlated with both financial and personal stress (Weatherburn, 2011). Women who experience violence are known to suffer a variety of adverse outcomes, including mental and physical illness and increased suicidal tendencies (Vachher & Sharma, 2010) (Loxton et al., 2006) (Taft et al., 2004). Past research has also shown that victims of violence are vulnerable to revictimization and have a greater chance of perpetrating violence on others. They also experience traumatic and debilitating physical and mental health consequences. Women's emotional and economic dependence have been found to be strong contributing factors towards their increased trauma (Varma et al., 2007). Women who experience systematic abuse have a larger likelihood than men to develop depression and other mental health consequences. More specifically, in the Indian context, factors of violence associated with poor mental health include dowry harassment, harsh physical punishment during childhood, having witnessed parental violence and substance abuse in the spouse (Dhavan, 2017; Bhola et al., 2016). Women who lived in poverty and/or were less educated were also found to be at increased risk of experiencing poor mental health. These women are faced with enormous social, physical and economic stresses, which in association with the experience of domestic violence are likely to increase their vulnerability to mental morbidities (Patel et al., 1999). The most frequently reported mental health consequences of intimate partner violence are depressive symptoms, anxiety

disorders, post-traumatic stress disorder (PTSD), somatization and substance use (Carbone-López et al.,2006) (Chandra et al.,2009).

## **THE ROLE OF WORK IN CAUSING OR AMELIORATING STRESS**

In the recent decades a number of research studies have been conducted, in women's overall life circumstances and their relation to women's health status. Paid employment in particular, has been considered an important part of women's living conditions as the number of women entering the labour market has grown constantly over the past few decades (International Labour Office, 2016). Research on the relationship between women's social roles and mental health has been ambivalent. In general, women's work is associated with better health. Despite that, the integration of more and more women into the regular workforce has resulted in considerable changes in their traditional roles which may cause / contribute to health problems. Specifically, the multiple roles that women perform in their families and in the society put them at greater risk than others for experiencing mental health related problems.

The amount and quality of leisure time distribution between the genders is a remarkable index of how women get burdened with stress for either natural or social obligations.

Women now bear a "dual burden" as they function both as providers and carers in the family. Absence of reciprocal and joint emotion management within family is a nagging stressor for women which can be physically both and psychologically draining.

The effect of multiple roles on women's psychological wellbeing remains controversial. Although it is well established that women's social roles affect their mental health, there is a lack of clarity about whether these effects are beneficial or detrimental. Existing theoretical understanding in this area proposes two competing theoretical perspectives. The role/job strain theory proposes that due to the limited time and energy each person has, women with multiple roles are more likely to experience 'role conflict'. The role/job strain model postulates that a combination of high psychological demands with low control at work leads to mental and physical illnesses (Karasek & Theorell, 1990). Contrastingly, the opposing theory

suggests that performing multiple roles results in benefits for the women, and that each additional role brings in benefits in the form of increased social contacts and self-esteem and this results in better health and psychological wellbeing (Waldron et al., 1998).

In general, however, women are more often than men, exposed to some psychosocial risk factors at work, such as negative stress, psychological and sexual harassment and monotonous work (Arcand & Labreche, 2000). Owing to their relatively lower status in the work pyramid, women tend to have less control over their work environment, and consequently, more commonly experience work-related fatigue, repetitive strain injury, infections and mental health problems than men (Ostlin, 2002; Artazcoz, 2004).

Women are particularly exposed to certain specific organizational risk factors such as excessive workload, lack of reward, unfairness and conflict of values.

According to the World Health Organization occupational or work-related stress is defined as “the response people may have when presented with work demands and pressures that are not matched to their knowledge and abilities and which challenge their ability to cope”. With specific reference to the Indian context, occupational stress is caused by an imbalance between work and family life. This imbalance arises due to various factors including mental harassment, sexual harassment, discrimination in the form of deprivation of promotion and growth opportunities and denial of their right of equal pay, lack of safety, lack of family support, insufficient maternity benefits and job insecurity. Additionally, sources of work stress, such as role ambiguity, relationships, tools and equipment, lack of autonomy, career advancement, job security, workload and work/home interface have been implicated in affecting family functioning.

According to Maslach, excessive demands exhaust an individual’s energy to a great extent. Women’s access and involvement in the workforce has led to them taking up multiple roles and multiple responsibilities (Maslach, 2006). Women play several simultaneous roles while men tend to play sequential roles. Working women are required to take charge of tasks on par with men at the workplace and in the home front. Women do more childcare, are in charge of caring for the older persons and also manage most of the household work while men work primarily at the workplace and do have more leisure time. A mismatch involving a lack of

appropriate rewards for the work done has an impact on the emotional wellbeing of people in general. This is more so in the case of women, as in most countries, women receive lower wages for comparable levels of work and education and are more likely to be engaged in low-paid employments.

Furthermore, women earn less than men in spite of holding similar positions, qualifications and experience due to discrimination and partial treatment at work. Lack of recognition and appreciation of hard work is closely associated with feelings of ineffectiveness, in addition to lack of intrinsic rewards (Salah, 2016).

Gender-specific work stress factors, including sex discrimination and balancing the work and family demands, may have an effect on women employees above and beyond the impact of general job stressors such as job overload and skill under-utilization. Discriminatory barriers to financial and career advancement have been linked to more frequent physical and psychological symptoms and more frequent visits to the (UK Essays, 2013).

Gender discrimination and unequal treatment raise multiple barriers to women's career opportunities and their wellbeing (Dubbelt et al.,2016). While it is emotionally draining, it also simultaneously creates a non-conducive work environment. With the increasing awareness and penalization of gender-based discrimination, women are subjected to subtler forms of sexual harassment and gender discrimination that negatively impact their morale, performance and opportunities for growth (Fink, 2017; Bernstein & Lenhart, 1993).

Besides overwork, women experience a role conflict that is an outcome of the 'psychological effects of being faced with multiple incompatible / contradictory expectations and demands' (Unger & Crawford, 1996). Women feel internally burdened to prove themselves as workers, wives and mothers and also to achieve 'all-round perfectionism' in all these roles which might ultimately lead to a burnout. The risk is further heightened when there is a lack of support from the spouse, extended family members and a lack of personal space and time.

In recent times, a growing interest in understanding quality of life issues and in better balancing of personal and work lives for both genders has emerged, which focuses on redesigning work and relaxing the work-family boundary in order to enable all workers to better integrate their work and personal lives.

## THE NATURE OF STRESS IN DIFFERENT LIFE STAGES IN WOMEN

Women tend to experience varied stressors during each stage of their life in addition to the regular stressors of life. The major sources of stress during each life stage are briefly discussed in this section.

### Adolescence and youth

Stress accounts for a sizeable proportion of variance in body image, and it is strongly associated with the gender of the individuals and their self-esteem. Further, particular domains of stressors relate to the body image differently: while peer pressure and school attendance were significant correlates of body image for both genders, prospective ambiguity and romantic relationships were significant only for males. Among young people, poor body image is a risk factor for mental health problems such as depression and eating disorders. While a poor body image could lead girls to develop eating disorders, boys were more likely to resort to steroid use and overtraining.

### Pregnancy

There are several identified causes for women experiencing stress during pregnancy. These include discomforts of pregnancy like nausea, constipation, tiredness, backache, mood swings and other reasons such as financial problems, experiencing abuse, major illness or death in the family and fear of labour and birth. Globally, low material resources, unfavourable employment conditions, heavy family and household responsibilities and strain in intimate relationships are some of the stressors that are identified as commonly affecting women during pregnancy. (Khosla et al., 2005), and pregnancy complications (Woods et al., 2010). Further, experiencing stress during pregnancy may in turn lead some of the women to resort to health-risk behaviours such as smoking, drinking alcohol or (ab)using other substances / drugs as a means of alleviating stress.

High levels of stress during pregnancy may result in negative consequences of poor birth outcomes and may affect the infants' development. Anxiety and stress during pregnancy are associated with shorter gestation, adverse foetal neurodevelopment, preterm birth and low birth weight (Dunkel et al., 2012). Other complications include pre-eclampsia, gestational diabetes, low APGAR scores and neonatal intensive care (Judd et al., 2014).

## **Motherhood**

Lack of sufficient time to spend with the child, financial stress posed by the child, demand of protective care from the child, early parenting, difficulty in saving energy to take care for themselves, worry about children's behaviour and social development are the common causes of stress for mothers. Adolescents are at high risk for difficult maternal maladjustment (involving fewer positive feelings about motherhood, decreased infant care and low parenting competency) and high postpartum maternal distress if they experience high stress during and after pregnancy (Holub et al., 2006).

## **Mid-life issues**

Hormonal changes of menopause, children's health, parenting, relationships with family members, caring for the sick relatives, lack of time for oneself, insufficient income, unemployment, lack of confidence and lack of sleep are the multiple sources of stress among midlife women. Loss of money, professional and occupational opportunities causes reduced self-confidence. Midlife women who have little or no support from the family or social networks, the results are devastating financially, psychologically and socially. Women in the midlife phase, who experienced a greater amount of stressful life changes and had higher body mass index scores, had reduced sleep in terms of the duration and higher health stress, which resulted in lower life satisfaction (Darling et al., 2011).

## **Menopause**

Menopause is a normal developmental transition that all women undergo with progressing age. From a biomedical perspective, the menopausal process is depicted as the deterioration of women's ability to reproduce. During menopause, the levels of estrogen in the body begin to drop and this in turn has an impact on the levels of cortisol. Cortisol is the "stress hormone," which influences, regulates or modulates many of the changes that occur in the body in response to stress. Stress during menopause has been linked to an increased risk of osteoporosis and cardiovascular disease and a greater frequency of vasomotor symptoms (Agarwal & Doshi, 2013).

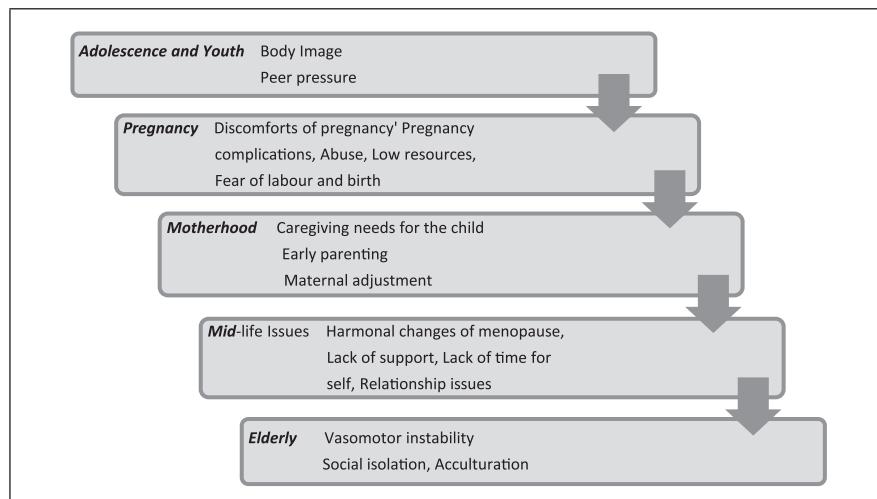
However, there are other factors as well, that are fundamental to the menopausal transition, and more than just biological changes need to be considered in understanding how women experience menopause. High stress, anxiety and depression have been identified to potentially worsen menopausal symptoms. In

addition, when women reported having a less satisfying marriage, low perceived social support, more perceived conflict in the relationship, and more distress related to self, husband, and family, they were found to report more menopausal symptomatology (Fielder & Kurpius, 2020).

### **Ageing**

Menopausal symptoms caused by Estrogen depletion causes increased depression and vasomotor instability. Older women who have poorer health, have few close friends, who have experienced more stressful life events and have felt dissatisfied with the help received from the family members tend to feel more depressed than others. For older adults, chronic illness, disability, or the loss of a spouse can be a source of prolonged stress (Rook & Charles, 2017). Other sources of stress may involve money, change in living situation, or family problems. Factors like immigration, language barriers, acculturation, financial hardship, social isolation and splitting of the household are identified as risk factors for depression among older women (Mui & Kang, 2006). Overall, stress can have varied effects in older persons including fatigue, loss of memory and concentration, inability to fight off or recover from illness, increased risk of chronic diseases such as heart disease and cancer, irritability or moodiness and excessive consumption of alcohol.

**Fig.1 Nature of Stress across different life stages in women**



## MANIFESTATIONS OF STRESS IN WOMEN

Studies on women experiencing premenstrual syndrome (PMS) have shown that these women exhibit blunted cortisol stress responses irrespective of the menstrual phases, as indexed by the cortisol levels across time, area under the curve with respect to ground (AUCg) and peak change scores of cortisol. Measurements indexed by cortisol levels across time, AUCg and peak change scores of heart rate were found to be smaller in women tested during the late luteal phase than during the follicular phase (Huang et al., 2015). Furthermore, hypo-reactivity of the hypothalamic-pituitary-adrenal (HPA) axis may be pathologically relevant to premenstrual syndrome because it predicts heightened PMS severity.

Mental illness occurring during pregnancy would increase the risk of obstetric and neonatal outcomes. Women experiencing mental illnesses during pregnancy are at a greater risk for developing gestational diabetes or pre-eclampsia and for having preterm birth of the infants (Judd et al., 2014), shorter gestation and adverse foetal neurodevelopment (Wadhwa et al., 1993), low birth weight and small for gestational age infants (Hoirisch-Clapauch et al., 2015).

Women with posttraumatic disorder due to childhood sexual abuse have exhibited with raised T3, TT3 levels and modest reductions in thyroid stimulating hormone (Friedman et al., 2005).

Interpersonal stress is associated with increase in disease activity among Rheumatoid Arthritis women. Pain from joint tenderness also was related to a decrease in stressful events one week later. Women with better relationship with the spouse did not have increased disease activity after an episode of interpersonal stress. Depression may be associated with increased pain in people with Rheumatoid Arthritis and Osteoarthritis and for those with only Rheumatoid Arthritis it may be related to elevations in stress and increased reactivity to stress and pain (Kwiatkowska et al., 2018; Zautra et al., 1994).

### Resilience and Coping with Stress in women

Not all women who experience psychosocial stressors in their lives develop mental health problems. Among the protective factors we find, for example, more education, political involvement, spirituality, the existence of an inner locus of control and self-reliance, family ties, human security, emotional disclosure to others (Veronese et al., 2019; Andu et al., 2018; Arcel et al., 1998).

It is important to study the resilience factors and their association with the prevailing culture, but there is still a lack of research in order to understand the positive aspects and protective function of a given cultural background and so it is important not to focus only on the negative impact of circumstantial stressors on different female populations.

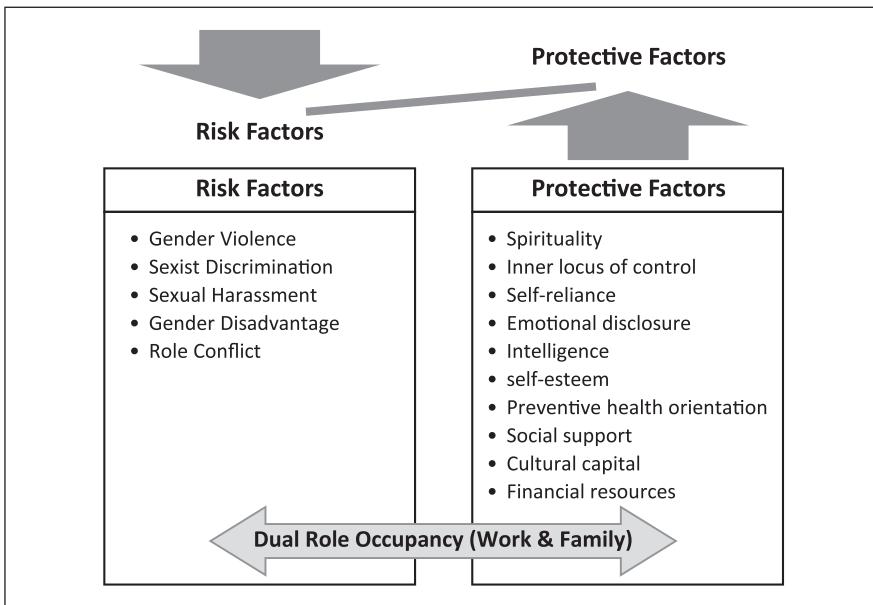
There has been a general tendency to focus on the negative and pathological impact of existing traumatic and societal factors and less on the resources these women possess; the coping styles and cognitive styles utilized, the defence mechanism used, and social involvement of women to adapt to changed life circumstances or a new cultural context.

Antonovsky (1988) developed a theory regarding psychological dimensions that affect health – a sense of coherence. The sense of coherence refers to an enduring attitude and measures how people generally view life and identify and use their general resistance resources (such as money, intelligence, self-esteem, preventive health orientation, social support and cultural capital) in stressful situations and to maintain and develop their health. The SOC consists of three dimensions: (i) ‘comprehensibility’ or the extent to which a person can make sense of internal or external stimuli; (ii) ‘manageability’ or the extent to which one recognizes that resources are available and (iii) ‘meaningfulness’ or the observation that life is meaningful and worth living despite its hardships.

The process of supporting women involves empowering women by enabling them to:

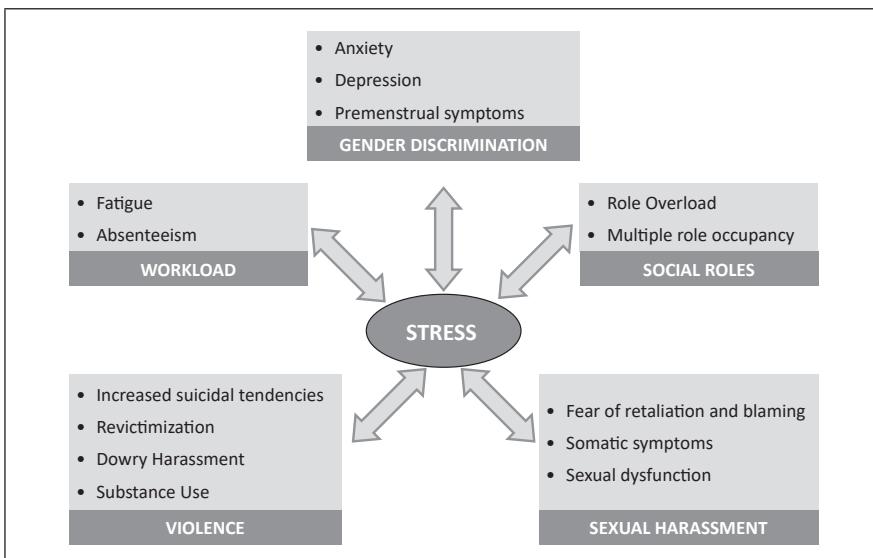
- Analyse their situation from an age, gender and diversity perspective
- Access information on their rights
- Define their own priorities and
- Take action they consider appropriate to address inequalities, realize their full capacity and utilize their skills, in order to attain a level of control over their own environment and livelihood

Fig.2 Risk and Protective factors for experiencing stress among women



### The Stress Framework

Fig.3 Framework for understanding stress among women



## CONCLUSIONS

It is important to study the impact of stress on women.

Various factors such as inequalities in life chances, differential exposure and multiple role occupancy and vulnerabilities like gender-based discrimination, harassment and violence are specific causes that make women more susceptible to experiencing stress.

Although employment in general has been associated with better health among women, their increasing integration in the regular workforce with the concurrent burden of their traditional roles puts them at a risk for experiencing mental health related difficulties. The sources of stress experienced and the nature of responses to the same varies depending on the stage of life of the women.

However not all women who are exposed to these stressors necessarily face negative outcomes. Protective factors and resilience provide a buffering effect to the experience of the adverse outcomes of stress.

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## **STRESS IN CHILDREN AND ADOLESCENTS**

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### **OUTLINE**

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| 1. INTRODUCTION                                | 2. STRESS DURING CHILDHOOD   |
| 3. PARENTING STRESS AND CHILD MENTAL DISORDERS | 4. PREVENTION AND MANAGEMENT OF STRESSORS DURING CHILDHOOD AND ADOLESCENCE |
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## **INTRODUCTION**

Nearly 50% of all lifetime mental disorders have an onset before late adolescence. Stress plays a role in the onset of many psychiatric disorders. Stress plays an important role, even children and adolescents. Manageable stress during childhood strengthens them to grow as healthy adults, while toxic stress overload can impact their sensitive developing neurobiological systems, with manifest ill effects on both physical, and mental health as they grow into adults. In this chapter, we try to define stress as relevant to children and adolescents and give an overview of the role of stress on neurobiopsychological systems at various developmental stages of children. We will also look at parental stress and its relation to childhood-onset mental disorders. Finally, we outline interventions that can mitigate stress overload in children and stress in parents.

## STRESS DURING CHILDHOOD

*Definition:* Stress is defined variously. Stress can be any stimulus that disturbs homeostasis and makes the organism draw upon its energy and resources to restore homeostasis. Stress can be internal or external; the latter is more crucial in child and adolescent mental health. In simple terms, an undesirable environment can be external stress (Dhama et al., 2019). The negative emotional state identifies stress that it evokes.

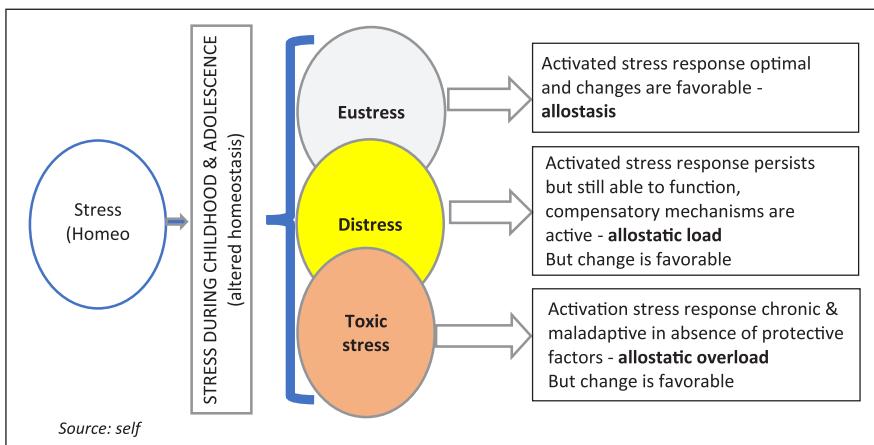
**Table 1. List of common stressors during childhood**

Child maltreatment	Childhood adversities	
Physical abuse	Poverty	Absence of a caring parent
Emotional abuse	Witness to trauma,	Presence of an antisocial parent
Sexual abuse	Witness to domestic violence	Death of parent
Neglect	Discrimination Crimes in the neighborhood Migrant status Lack of access to universal health coverage Lack of access to education Societal acceptance for child labor, early marriages Sibling rivalry School bullying Harsh and punitive teachers	Psychiatric illness in a parent Substance abuse in a parent Chronic physical disease in a parent Chronic physical in the child Significant life events

### Stress during childhood

Whether the stress response is adaptive or maladaptive depends on the child's age when exposed to stress, stress frequency, and duration of the traumatic exposure, genetic susceptibility (Katz, et al., 2011)(Thompson, 2014). Multiple adversities in early childhood (Table 1) can have a cumulative dose-response effect, and after specific threshold, stress changes become maladaptive. Mild to moderate, short-lasting stressors strengthen the child's coping abilities (Thompson, 2014). Thus, some stress as a normal part of life is conducive to healthy development, while severe, chronic, and multiple stressors can be detrimental (Fig 1), leading to impaired physical and psychological health (Muscari, 2018).

Fig 1. Stress and its types based on its relation to stress response



Genetic makeup and epigenetic changes explain why some children develop mental health problems to negative environmental experiences, also known as the stress-diathesis model, and explain why not all respond favorably to interventions. Low activity of the enzyme mono-amine oxidase-A(MOA-A) increased the risk of developing conduct disorder and later antisocial personality disorder in the presence of childhood adversity. The effect of maltreatment on liability to the development of depression is moderated by 5-HTT (5 hydroxytryptamine transporter) gene. The presence of two short alleles of the serotonin transporter gene (5-HTT) associated with increased risk for developing depressive disorder, anxiety disorders, post-traumatic disorders in childhood adversity and predicts poor response to cognitive behavior therapy. The presence of two long alleles of serotonin transporter gene (5-HTT) is associated with decreased risk for developing anxiety and reduced risk of depression. However, it increases the risk for callous-unemotional traits seen in a subgroup of children with conduct disorder. Thus, gene-environment interaction is vital in developing resilience (Rutter's Child and Adolescent Psychiatry, 2015). However, in vulnerable persons, lower doses of stress can be detrimental, while higher amounts of stress can be detrimental for resilient persons. It is difficult to define what constitutes stress for the child because it is not restricted by the experience, but by the behavioral, cognitive, emotional responses it elicits. These responses are the result of stress-activated neurobiological systems (Cronin et al., 2015).

### **Stress during adolescence**

The most common sources of stress are low self-esteem related to appearance, feelings of inadequacy or having high expectations, interpersonal issues with peers, academic difficulties, Parental discord, changing school, chronic illness in the family, death of loved one, financial difficulties. Overstress leads to anxiety, withdrawal, aggression, physical illness, or poor coping skills such as alcohol or other substance use (American Academy of Child and Adolescent Psychiatry, 2019).

### **Stress response during childhood and adolescents**

Stress during childhood elicits stress response as in an adult. Primary mediators of this stress response seem to be changed in glucocorticoids, catecholamines, cytokines. The number of primary mediators released seem to be moderated by gender, age, and pubertal status. When active for long periods, primary mediators lead to secondary outcomes shown as neuroendocrine changes, immune, metabolic, cardiovascular, respiratory, and anthropometric markers. Tertiary outcome appears many years later due to continued maladaptive neurobiological changes in the form of increased susceptible to illness, developmental of chronic diseases and mental health problems (Condon, 2018). Secondary and tertiary outcomes are due to maladaptive stress response changes resulting from persistent or severe or multiple stressors (Fig. 2).

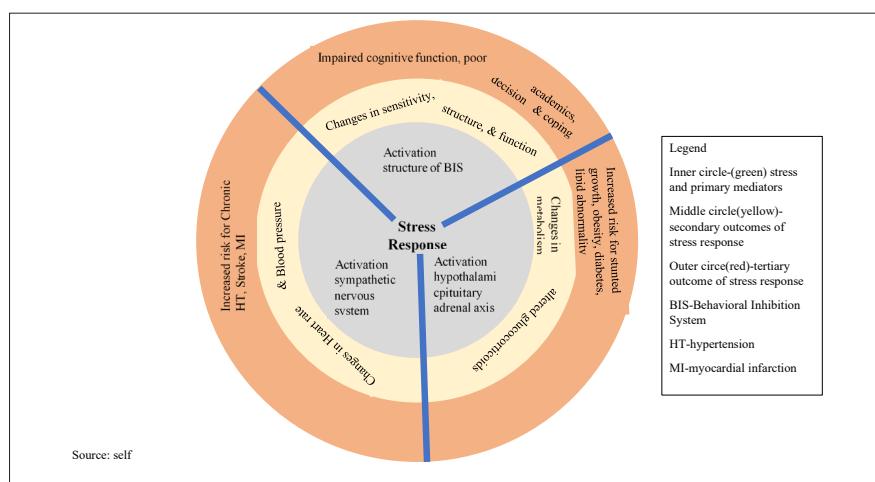
Significant neurobio-psychological changes in response to severe stress in the form of environmental adversity, also referred to as Bioecological model (Weems, 2015) are:

1. **Overactivation of limbic CNS structures** involved emotional response to fear: Hippocampus, amygdala, noradrenergic projections of the locus coeruleus, and serotonergic projections of the median raphe. These structures together form the Behavioural Inhibition System (Weems, 2015). On exposure to chronic stress structures of the corpus callosum, hippocampus and cognitive functioning are impaired. Corpus callosum myelination happens between 6 months to 3 years of age. During this sensitive period, any early childhood adversities affect corpus callosum development specifically, while the hippocampus is affected by adversity at all ages (Brietzke et al., 2012)..

2. **Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis** in the form of persistent higher levels of cortisol in the blood, disappearance of diurnal variation in cortisol release (normally with peak in the morning), in the long term it cortisol reaches lower levels and cortisol fails to increase in response to new stress (Blaisdell et al, 2019). This dysregulation also affects neuroendocrine, immune, metabolic, cardiovascular, respiratory, and physical development (Condon, 2018).
3. **Increased Psycho-physiological arousal:** There is excessive sympathetic overactivity manifest as increased heart rate, increased blood pressure, increased skin conductance for electricity and failure to maintain parasympathetic system. Along with this there is psychological arousal in the form of excessive fear, hyperarousal, negative emotionality together; these are known as negative disaster reactions (Weems, 2015).

These responses negatively influence physical performance, academic performance, and social performance (Blaisdell et al., 2019). Many of these changes become permanent and passed onto the next generation via epigenetics (Thompson, 2014). There is an increased risk for physical illness and mental health disorders like conduct disorder, depression, bipolar disorder, suicide, substance abuse, psychosis, and personality disorder (Brietzke et al., 2012).

**Fig 2: Primary mediators, secondary and tertiary outcomes of maladaptive stress response**



Childhood stress can be minimized by early responsive caregiving either by a biological parent, foster parent, or by other caregivers(Thompson, 2014; Blaisdell et al., 2019), and by secure attachment of the child with caregiver (Katz et al., 2011). Support for early responsive caregiving in reducing ill-effects of childhood adversity came from rodent experiments, where licking and grooming by mother rat led to the proper expression of glucocorticoid receptors the hippocampus in the baby rat within one week after birth and prepare the baby rats to respond better to stress in future(Maney & Szyf, 2005). From primate experiment, parental separation, peer rearing in monkeys showed that behavioural problems and socialization problems occur when they grow into adults (Suomi et al., 1976).

## PARENTING STRESS AND CHILD MENTAL DISORDERS

Literature evidence shows an overall bidirectional relationship between parenting stress and mental disorders in children and adolescents. Stress in parents is now differentiated into Parental Stress and Parenting Stress. Parental stress is defined as stress that parents experience because of childrearing and their social and environmental circumstances, responsibilities, and everyday life. The term Parental Stress acknowledges that there is a greater context for the stress parents experience (Belsky, 1984). While Parenting Stress is the stress that is felt in response to the demands of being a parent. Sometimes this stress is often experienced as negative feelings toward the self and toward the child or children. By definition, these negative feelings are directly attributable to parenthood demands (Deater-Deckard, 1998).

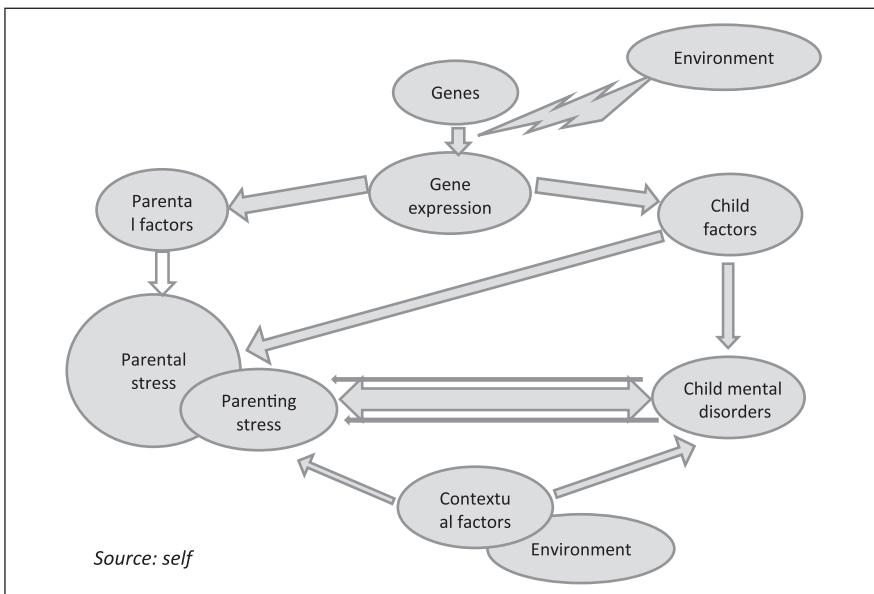
Child mental health disorders can be characterised as internalizing disorders or externalizing disorders. Important internalizing conditions include depressive disorders, anxiety disorders. Attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), antisocial personality disorder (ASPD), pyromania, kleptomania, intermittent explosive disorder (IED), and substance-related disorders are frequently referred to as externalizing disorders. Externalizing disorders are reflected by behaviour, while internalizing disorders are in the form of subjective distress.

Well-designed studies show bidirectional relation (Fig 3) between parenting stress and child mental health problems (Neece et al., 2012; Achtergarde et al., 2015). Force of direction is influenced by Parent-related, Child-related, and contextual factors (Achtergarde et al., 2015). Important parent-related factors that

influence the onset of child mental health problems are parenting types, parent education, parent personality, presence of psychopathology in the parent, and substance use disorder in the parent. Authoritative parenting is considered best with a good outcome; authoritarian parenting can lead to externalizing disorders in at-risk children, while permissive parenting style can lead to either internalizing or externalizing disorders in the children at-risk. Child-related factors that influence the onset of mental health problems in the child are age, gender, and temperament. Difficult temperament can elicit parenting stress, which increases the risk for the child in a vicious bidirectional pattern, increasing the risk of developing mental health problems in the child. Fearfulness and impulsivity are other temperament types that increase the risk for child mental health problem in interaction with the parent related factors. Contextual factors rely on the circumstances under which the parent-child or caregiver-child quality of interaction can influence child mental health problems (Achtergarde et al., 2015). Thus, parenting stress can be a source and the effect of a child's mental disorder. However, there are exceptions to this bidirectionality. Lohaus et al., (2017), assessed for the direction of the relationship between the child mental disorder and parenting stress in foster parents and biological parents in a case-control design. These children were exposed to adversities in the form of maltreatment or neglect, raised in institutes or foster care. Externalizing disorders in children predicted parenting stress in both biological and foster parents. While internalizing disorders in children predicted parental stress mainly in biological mothers. Thus, parenting stress can be different in father and mother. Parenting stress can be predicted by the presence of internalizing disorder in the child. In contrast, both parent-related and child-related factors contributed to the onset of externalizing disorders even in atypically developing children (Rodriguez et al., 2019).

The bidirectional relationship between parenting stress and child mental health problems implies that ways to reduce the strength of this bidirectionality is by teaching healthy Parenting practices, teaching specific coping strategies, interventions targeting behavioral problems in children, treating the family as unit, and changing the contextual factors (Cronin et al., 2015).

**Fig. 3 schematic diagram to understand the complexity of the relationship between parental stress and child mental disorders (for some, externalizing and internalizing disorders relationship can be unidirectional)**



## **PREVENTION AND MANAGEMENT OF STRESSORS DURING CHILDHOOD AND ADOLESCENCE**

### **Prevention of chronic stressors**

This can be achieved through government policies and larger public health initiatives that are aimed at reducing inequalities, reducing childhood adversities (poverty, discrimination, lack of shelter, lack of safety, lack of access to safe water, lack of access to universal health care, lack of access to education) (Condon, 2018).

### **Management of the effect of stress during early childhood**

**Early Responsive caregiving programs:** Review of programs suggest that programs that target responsive parenting in foster parents for very young children like ABC (Attachment and biobehavioural Catch-up) intervention, MTFC-P intervention (Multidimensional treatment foster care-for pre-schoolers), KITS intervention (Kids in the transition to school) show that they can help children grow out of the impact of childhood adversities and some studies show that dysregulated altered HPA axis normalizes in children (Blaisdell et al., 2019).

**Parenting Programs:** Quality of care that parents provide matters a lot, and it can prevent the origin of mental health problems in children as they grow. Ryan, O'farrelly and Ramchandani, (2017) reviewed important parenting programs like Incredible Years (for parents with children age 0-12 yrs), Triple P (for parents with children age 0-16), Parent-Infant Psychotherapy, Family Nurse Partnership (Young ≤19yrs first time mothers till the child is 2 years old), Video programs (Video Feedback to Promote Positive Parenting [12-36 months old], Video Interactive Guidance). These programs are useful in reducing parenting stress and show mixed results in preventing mental health problems in children. One limitation of these interventions is that they are used more by parents, having typically developing children (Neece et al., 2012).

Assuming the bidirectional relationship between parental stress and child mental health problems, there can be:

**Parent targeted interventions:** Stress management, improving coping strategies, enhancing parental support. There are two main types of coping strategies associated with the reduction of stress in parents: Primary control coping (includes problem-solving, emotional regulation, relaxation) and secondary control coping strategies (acceptance, cognitive restructuring) (Cronin et al., 2015).

**Child targeted interventions:** Interventions (pharmacological or non-pharmacological) that address externalizing or internalizing disorders.

*Parent-Child interaction targeted interventions:* This can be in the form of family therapy. In foster parents, they can be trained and supported, with strategies to manage externalizing disorders in children (Lohaus et al., 2017).

### **Management of stress in adolescents**

There is a role for parents in decreasing the impact of stress. The reduction can be made by non-judgmental listening, modeling stress management, supporting prosocial activities in adolescents. Adolescents can adapt some behavioral changes and techniques to reduce stress. They can learn to have more adaptive thoughts, relaxation exercise, involve learning new skills, maintain a good sleep routine, try to exercise and eat regularly, rehearse and practice situations that cause stress(for examples: class presentations, public speak, speaking to an authority) (American Academy of Child and Adolescent Psychiatry, 2019).

Recent systematic reviews have reported that Eye Movement Desensitization and Reprocessing (EMDR) and Trauma-focused cognitive behavior therapy (TF-CBT) can help treat children with PTSD and related comorbidities (Moreno-Alcázar et al., 2017; Neelakantan et al., 2019). However, there is a need to properly integrate these programs in foster care and in-home family therapy settings and the developmentally disabled population..

## CONCLUSIONS

Stress is something undesirable and which evokes negative emotions. Stress is a part of life; mild stress and short-lasting stress strengthen coping ability, more relevant in children. The Source of stress for children lies in the environment. Any childhood adversity can elicit human stress response: a neurobiological activation that involves brain structures, limbic hypothalamic-pituitary-adrenal axis, sympathetic nervous system Persistence of stress adds to allostatic overload, can have secondary effects on physical growth, academic, socialization. In the long run, it leads to increased susceptibility to physical illness and mental health disorders. Allostatic overload can be decreased by early responsive caregiving in children. Child mental disorders can have a bidirectional relationship with parenting stress. Child and parent-related factors and contextual factors influence the direction and strength of this relationship. Interventions targeted at parents, children, and modifying contextual factors will help weaken the relationship between parenting stress and child mental disorders. Quality of care by caregivers is important.

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## **STRESS AND AGING**

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**OUTLINE**

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| 1. INTRODUCTION                            | 2. FACTORS CONTRIBUTING TO STRESS IN LATE LIFE            |
| 3. MANIFESTATION OF STRESS IN OLDER ADULTS | 4. INTERVENTIONS TO DECREASE STRESS LEVEL IN OLDER ADULTS |
| 5. CONCLUSIONS                             |   |

### **INTRODUCTION**

**a. Older adults' population in World and specifically in India:**

One of the greatest achievements of modern-day world is the increase in life expectancy. In India alone, the life expectancy has increased from 34 years in 1950 to 68 years in 2011. This achievement is due to the advances in medical sciences, ability to overcome threats and welfare measures by the respective countries. As a consequence, more number of people are living well beyond 60 years and resulting in population ageing. The United Nations defines a country as 'ageing' where the proportion of people aged over 60 years reaches seven per cent or more. By 2000 India has exceeded that proportion (7.7%), with current proportion of nearly 10% and is expected to reach 12.6% in 2025 (United Nations Population Fund, 2017; Ministry of Statistics and Programme Implementaton, 2016). Among the older adult population in the world, one-eighth live in India.

**b. Current situation of older adults in India**

Though we are successful in adding years to life, we have still not addressed the issues associated with old age and adding life to extra gained years. Old age is described by many as a period characterized by loss of friends, loss of income and loss of health. In India, nearly 70% of older adults stay in rural areas with a very low literacy rate of 43%. Older adults in India face several challenges in their late life. With changing family structure and increase in preference for autonomy and individualism, many older adults are left alone by the children. In addition, lack of adequate social security measures and lack of awareness about social welfare measures contributes to increased risk for the safety and well-being of the older adults. Many older adults are economically dependent, face neglect, deprived of their rights and basic needs. Deteriorating physical health and failing sensory system also adds to the problems. Older adults also face a challenge of going through daily hassles in this digital world (Mishra, 2020; Nidhi, 2019). All these issues contributes to significant stress for older adults and creates barriers for successful ageing.

**c. Old age and psychological stress:**

It is interesting to understand, whether ageing is associated with increased or decreased stress level compared to other age groups. There is a discrepancy in the literature on the perceived stress level in aged population. Few studies reported comparable stress level in young and old adults and few others reported increased stress in old age. Studies have found increased health-related stressors in older adults. In a study on 1,656 older adults (66–97 years) that used 10-item perceived stress scale (PSS), high stress level was reported in 7% with older women reporting higher stress level than older men (Osmanovic-Thunström et al., 2015). Studies that included healthy older adults reported less stress level, whereas studies on older adults with physical comorbidity, cognitive impairment and psychiatric illness reported higher stress level.

**FACTORS CONTRIBUTING TO STRESS IN LATE LIFE**

Psychological stressors are a public health concern as they are adversely associated with a negative impact on physical and mental health (Fig 1)

**a. Retirement**

Retirement is an important social life event. The age of retirement in India is usually 60 years. However it varies from 56 to 70 years depending on the rules

in different public and private services. This is an important transition after a structured daily work for many years in the service. This mean older adults have to leave their usual daily work which they had maintained for many years. Retirement leaves older adults with lack of regular work, decline of position in the community, income and companionship of work-place colleagues. In many individuals, retirement may also lead to shifting to a different locality or migration to their native places. All these factors may contribute to stress and despair in some of the older adults. A survey from China reported a differential effect related to the gender. This survey found retirement contributing to increased stress in women and reduced stress level in men (Chen et al., 2020). Robert Atchley, 1976 has classified stages of retirement into six stages (pre-retirement, retirement, disenchantment, re-orientation, retirement routine and termination of retirement. Studies from the West reported a positive impact of retirement on mental health. However, studies from the eastern world reported a negative impact of retirement. Few studies reported that older adults who continue regular activities (either as hobbies or part-time) remain well compared to those who do not involve in any kind of activities (Mukku et al., 2018; Oksanen et al., 2011).

**b. Loss of status and role transitions**

Old age is associated with changes in social status and role transitions. Many people who have been the head of the family for many decades, after reaching 60's may have to slowly give away their responsibilities. Head of the family is usually involved in making important decisions, financial investments, designating the task to other family members and enjoying the respect from other family members. Older adults are also head of several villages in our country. As age advances, there will be a change in power dynamics with children or younger sibling taking over the role of head of the family (Deeg et al., 2018). Nearly 60-75% of all older adults are economically dependent on others, usually their children. Even those with pensions find their economic status lowered after retirement. This transition might happen smoothly in some families, however, in a proportion of families, this might occur either abruptly or involuntarily. These role transitions is known to contribute to stress in older adults. The loss of status due to retirement, decreased earning capacity and decreasing physical health are likely to contribute significant stress for older adults..

**c. Bereavement and Grief**

Bereavement refers to the loss of close relative, object, or position. Majority of older adults experience bereavement. One of the significant losses in old age is the demise of close relatives and friends. Among them, demise of spouse is seen as a major life event and contributor of grief in older adults. Older adults also experience anticipatory grief in the situations, when they develop life-threatening illness. Studies also reported grief in older adults during the initial stages of cognitive impairment and dementia. As per the 2011 census, after 80 years of age, 30% of males and 69% of females are widowed in India (Ministry of Statistics and Programme Implementaton, 2016). Bereavement and grief are significant contributors to stress in older adults..

**d. Physical illness (chronic medical illness) contributing to stress**

Older adults often suffer from chronic medical illness. These include hypertension, diabetes, osteoarthritis and ischemic heart disease (Ingle & Nath, 2008). Many of the chronic medial illness in older adults are not curable and may require long term medication and life style modification. This may contribute to stress in many older adults. Other issues such as requirement for regular adherence to medication and monitoring may also lead to increased burden and stress in older adults. In addition, the requirement of regular check-ups with their family physician and the related medical expenses may have a huge impact. This is especially important considering the fact that majority of older adults work in the unorganised sector and do not have adequate medical benefits or insurance. Other important issues are the discomfort, pain and disability arising from medical illness which in turn may contribute to high stress level. There is also bidirectional relationship between the stress and medical illness (Turner & Kelly, 2000) with each having adverse impact on the other.

**e. Adverse psychosocial situations**

A variety of psychosocial stressors in late life may hinder health-related quality of life which is crucial for successful aging.

**i. *Living alone***

In India, as per the 60th round of the National Sample Survey, nearly 5% of older adults live alone and another 4% live with distant relatives and others (Ministry of Statistics and Programme Implementaton, 2016). The proportion of older adults

living alone in India is much lower when compared to other developed countries. In the USA nearly 30% of older adults live alone (Stahl et al., 2017). However, the economic development and increasing migration of younger adults to urban cities within or outside the country will contribute to increase in the proportion of older adults living alone in future. There are several challenges for older adults living alone. These include social isolation, boredom, lack of support for daily requirements, lack of emotional support, increased physical demand to sustain themselves (Chou et al., 2006; Lim & Kua, 2011). Older adults living alone have to face everyday hassles required for independent living. Older adults living alone are also at risk of cheating and exploitation (Goswami & Deshmukh, 2018). All these factors lead to insecurity, uncertainty, loneliness and contribute to the higher stress level.

ii. *Living in residential care*

Traditionally India is known for the joint family system which prevailed for centuries. In this joint family system, the offspring when they grew up are expected to take care of aged parents. With modernization and globalisation, there are changes in this living structure with the emergence of nuclear families. The children move out of the homes in pursuit of education, employment and prefer to stay as a nuclear family. This leaves older adult couples at villages or urban places alone. Many older adults, as their physical health decline seek for a place which provides assistance and security. This may lead to older adults to move to old age homes, assisted living facilities and residential care facilities. In India there are more than 1000 old age homes and this number is rapidly increasing (Menezes & MariamThomas, 2018). Older adults living in residential care facilities may face many unpleasant experiences. These include conforming to tight schedules, poor facilities, overcrowding, lack of personal care, stereotyped life, and separation from the family. Though residential care facilities provide support and security, often the living experience might be unpleasant and thus may contribute to stress in older adults (Dubey et al., 2011; Menezes & MariamThomas, 2018; Walker & Paliadelis, 2016).

iii. *Ageism*

Ageism is broadly defined as prejudice or discrimination towards people due to their age (Nelson, 2005). Ageism manifests in the form of negative attitudes towards older people, old age and the ageing process, discriminating and treating older people unfairly. Ageism is another problem seen with older adults across the

regions contributing to stress. In surveys of thousands of adults aged 52 years or older, 35% of those living in England and 29% of those in the USA experienced age-related discrimination (Rippon et al., 2015). Studies have found discrimination based on age having a negative impact on the mental health and well-being in older adults. Ageism act as barriers for participation and achieving to the fullest potential in older adults. The ageism might prevent older adult form healthy behaviours and contribute to poor physical and mental health (Jackson et al., 2019; Lyons et al., 2018)

iv. *Economic constraints*

The Sample Survey conducted by the National Sample Survey Office in 2004 reveals that 65 per cent of the aged persons had to depend on others for their day-to-day maintenance. As per the population census 2011 data, 66% of elderly men and 28% of elderly women in rural continue to work either as main or marginal worker for their financial needs, whereas in urban areas, 46% elderly men and about 11% of elderly women continue to work (Ministry of Statistics and Programme Implementaton, 2016; Sanjeev Bakshi & Prasanta Pathak, 2016). These reveal that a significant proportion of older adults face financial crisis in old age. Lack of pension schemes in un-organised sectors, lack of schemes to generate home-based employment, lower pay for older adults at workplace are contributors for decreased financial status. Other issues such as gifting property to children, neglect and abandonment often lead to the economic crisis. A minority of older adults in India, quickly spiral down to extreme poverty and resort to beggary. Though there are anti-beggary laws, however many older adults are noticeable at religious places doing this activity. Financial ability determines the health care of older adults as the majority of older adults do not have health insurance schemes. This financial status is an important factor determining the stress level and mental health of older adults (Mishra, 2020).

v. *Abuse/neglect*

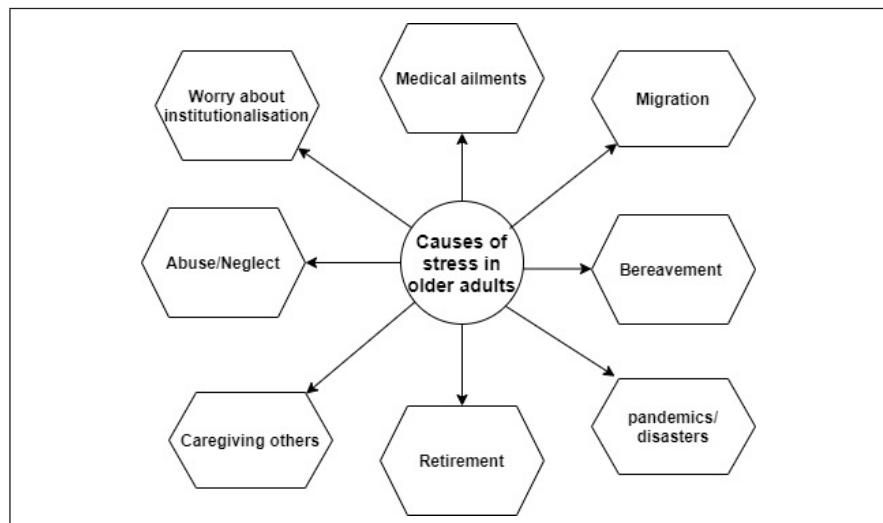
Elder abuse is defined as “A single or repeated act or lack of appropriate action, occurring within any relationship where there is an expectation of trust which causes harm or distress to an older person. It can be of various forms: physical, psychological/emotional, sexual, financial abuse and neglect (WHO definition).” As per the multicentre survey by HelpAge India in 2018, one-fourth of older adults have experienced abuse in India (A HelpAge India Report- ELDER ABUSE IN INDIA, 2018). Some of the risk factors for abuse include the financial status of

elderly, cognitive impairment, physical dependency, substance use in the caregiver, nature of the relationship between carer and caregiver, disruptive behaviour in care recipient and depression in caregiver. Neglect and abuse have long-lasting effects on the psyche of older adults. Majority of older adults will not reveal or notify the concerned authorities about the abuse due to the fear of the negative effect on family honour and also lack of awareness. Many times, offenders of abuse are close family members. Though elder abuse is prevalent, many times, older adults continue to suffer due to lack of awareness and family sanctions (Evandrou et al., 2017).

#### vi. Disasters/Pandemics

The World Health Organisation defines a disaster as an “occurrence, disrupting the normal conditions of existence and causing a level of suffering that exceeds the capacity of adjustment of the affected community” (World Health Organization, 2002). A pandemic is a disease or an outbreak that spreads across countries or continents. A pandemic can lead to a disaster which not controlled well. Some of the important disasters in India are Bhopal gas tragedy (1984), Orissa super-cyclone (1999) and Tsunami (2004). In terms of pandemics, Asian cholera and the current on-going COVID-19 have demonstrated the extent of the disruption of the normal life in such disasters. Older adults are one of the most affected group in disaster and pandemics.

**Figure 1. Sources of stress in older adults**



Disasters are known to have serious impact on mental health (Kar, 2010). Older adults due to their constitutional vulnerabilities, associated physical morbidities and decreased help-seeking behaviours have higher risk of negative outcome during and after the disasters. Studies reported that older adults are at high risk of mental health issues compared to other age groups though there are few reports contrary to this finding (Viswanath et al., 2012; Philip & Cherian, 2020; Rafey et al., 2016). In a recent survey from the USA in the ongoing COVID-19 pandemic, nearly 36 % of older adults reported increased mental stress (Emerson, 2020)..

## MANIFESTATION OF STRESS IN OLDER ADULTS

Psychological stress triggers a stress response to restore the homeostasis. The stress response is known as fight or flight response as proposed by Walter Cannon. The main neural centre for stress response is the hypothalamus. The hypothalamus activates two important pathways. One is sympathetic pathway activation, which in turn stimulates the adrenal medulla and lead to the release of catecholamines. The second pathway is the activation of pituitary-adrenal axis through corticotrophin releasing hormone that lead to release of cortisol. Though these responses are beneficial in the short-term to overcome the acute stress, but not helpful in the long term. Prolonged stress will have pathological activation of sympathetic and pituitary adrenal axis with negative impact on mental health and physical health. Chronic stress lead to decreased immunity and impaired wound healing. In addition, the age related changes in the physiological systems in handling chronic stress in older adults will contribute to further poor health (Vitlic et al., 2014). (fig.2 and fig.3)

Figure 2: Age related to changes in pathways that are involved during stress response

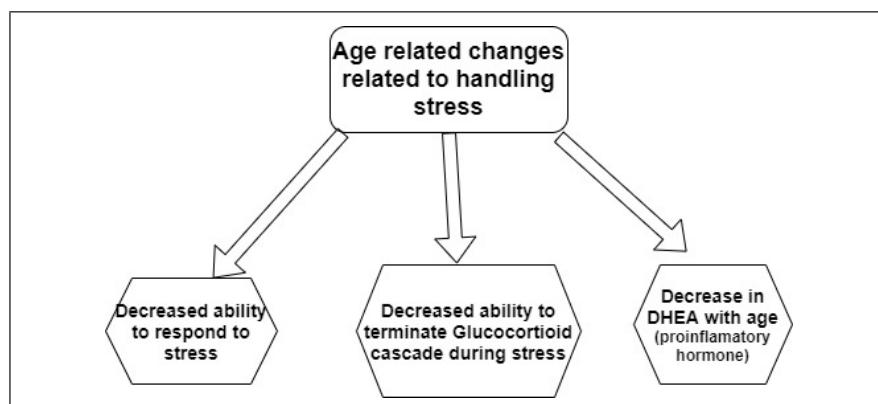
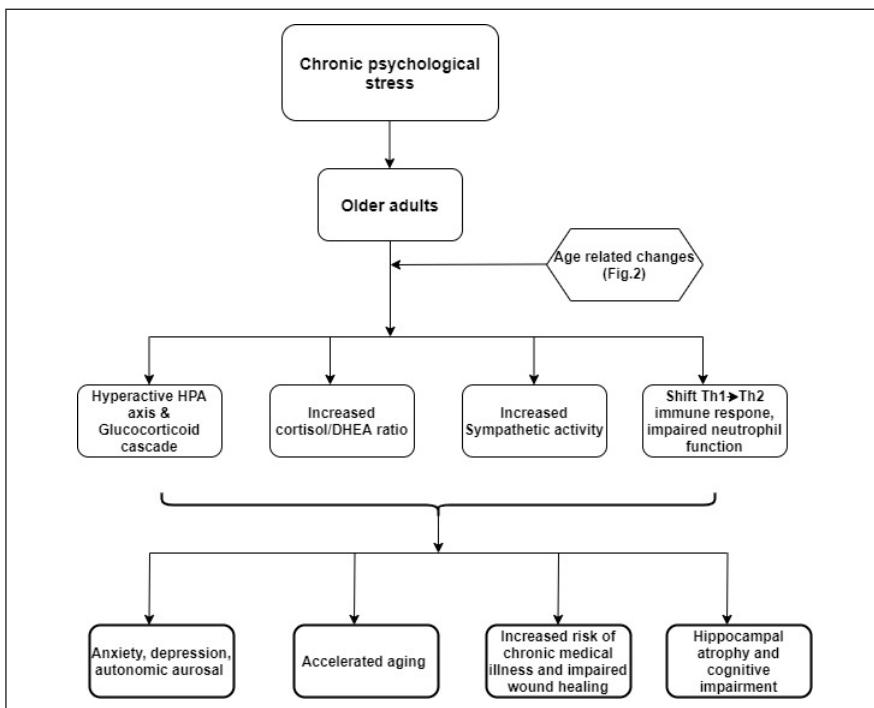


Figure 3: Impact of chronic stress on mental health and physical health



#### a. Mental health issues

Older adults who face stressors are at high risk of psychiatry illness. Studies have reported an inverse relationship between stress level and health-related quality of life (De Frias & Whyne, 2015). The signs of stress of older adults can present as changes in eating habits, irritability, indifference, withdrawal, decreased grooming, somatic pains, headache, anxiety symptoms, insomnia, decreased energy level, impaired attention and frequently falling ill. The common psychiatric illness includes anxiety disorder, adjustment disorder and mild-moderate depression. The severe psychiatric illness can be major depression, acute psychosis, post-traumatic stress disorder and substance use disorder.

Suicide risk is another important mental health issue in older adults. The suicidal rates are higher in older adults across the regions compared to other age groups (Shah et al., 2016). The psychological stressors in the form of widow status, bereavement, social isolation, physical pain psychiatric disorders and comorbid physical illness increase the suicidal behaviours in older adults (Conejero et al., 2018).

**b. Physical Health issues**

Stimulation of the sympathetic nervous system by chronic stress causes an elevated heart rate and cardiac output. In addition, there is also an activation of the renin-angiotensin-aldosterone system. Increased activity of the sympathetic nervous system plays a part in the development of insulin resistance, impaired glucose and derangement in lipid metabolism. These metabolic abnormalities increase the risk of hypertension and diabetes mellitus (Hackett & Steptoe, 2017). However, in a meta-analysis that included seven prospective studies, there was no association between work-related stress and type II diabetes mellitus, however the association was significant in females (Sui et al., 2016). These studies took into consideration only work-related stress but not any stressful life events. In a prospective 20-year follow-up study, stressful factors such as employment insecurity, unemployment and low self-reported job performance found to independently predict hypertension incidence among men (Levenstein et al., 2001). In a meta-analyses of prospective observational studies found that social isolation and loneliness were associated with a 50% increased risk of incident Cardiovascular disease (CVD) events (pooled relative risk 1.5) (Steptoe & Kivimäki, 2013). Studies on adults with work stress or personal life stress reported to have a 1.1-fold to 1.6-fold increased risk of incident coronary heart disease and stroke (Kivimäki & Steptoe, 2018).

Apart from vascular and metabolic disorders, psychological stress is associated with increased risk of cancers and progression of cancers. Psychological stress lead to alterations immune response, one among them is a decline in NK cell response. These immune cells are usually involved in eliminating tumour cells and viral infected cells. This lead to the risk of proliferation of tumour cells and spread. Psychological stress is also known to alter the DNA repair process (Soung & Kim, 2015). In a recent meta-analysis, Kruk et al. reported that severe life events, anxiety, depression, poor social support were significantly associated with the increased risk of breast cancer. There is no consistent association with other type of cancers. There is greater evidence for cancer progression, metastasis and higher mortality in patients with psychological stress (Kruk et al., 2019).

## **INTERVENTIONS TO DECREASE STRESS LEVEL IN OLDER ADULTS**

**a. Increasing awareness about their right and laws**

The article 41 of the constitution lays down that the “State shall provide within the limits of economic capacity and development, make effective provision for securing

the right to work, to education and to public education in case of unemployment, sickness, old age and disability". To safeguard the right of older adults, there are certain legal acts that have been brought in India. The Maintenance and Welfare of Parents and Senior Citizens Act, 2017 was enacted to provide maintenance support to parents and senior citizens. This is a landmark act to protect the rights of older adults. Under this act parents or senior citizens can claim maintenance from their children or grandchildren. The Act also proposed for establishments of the tribunals and old age homes in every district ('The Maintenance and Welfare of Parents and Senior Citizens Act, 2007|Legislative Department | Ministry of Law and Justice | Goverment of India', 2007). Thought the MWPS Act, came to existence more than a decade ago, many older adults are not aware of it. The Rights of Persons with Disability Act (RPWD), 2016 is another act to protect the right of older adults with disabilities. Under this act, older adults with disability has the right for guardianship, right to protect against abuse or exploitation and accessing rehabilitation facilities (Math et al., 2019). Mental Health Care Act (MHCA) provide right to access mental health care for all citizens. There is a provision under MHCA, 2017, that state need to provide shelter and rehabilitation facilities for person with psychiatric illness (Sivakumar et al., 2019). National Legal Services Authority (NALSA) scheme under the legal services act, 1987 is another policy brought to increase the awareness about the right, laws and access to various government schemes and programs to older adults. Under this scheme, older adults can avail free legal aid. These are some of the legal measures to mitigate the stress in late life ('Nalsa (Legal Services to Senior Citizens) Scheme - National Legal Services Authority', 2016).

#### **b. Barrier-free environment for older adults**

Enabling environment is very important for stress free independent living of older adults. Older adults due to age related issues and disability need environmental modifications for accessing any service and for their daily living. In India, there are provision for separate queues for older adults in hospitals, provision of wheelchairs, speciality clinics for older adults. In addition, there are provisions for specific seats reserved for older adults in bus and trains. There is a need to implement these measures effectively and extend these elderly friendly measures to other settings. There are also initiatives in terms home structure modification for older adults and especially for patients with dementia. A barrier free environment certainly has role in reducing the stress in older adults (Yarmohammadi et al., 2019).

**c. Promoting Healthy behaviours**

Healthy behaviours are important for older adults to maintain their physical health as well as their mental health. Physical activities such as exercise, walking, swimming are to be encouraged. Mind-body based activities such as mediation and Yoga are known to have multiple benefits. Other activities such as gardening, painting, learning a musical instrument and writing or reading novels are some of behaviours known to reduce stress (Snowden et al., 2015).

**d. Promoting social networks**

Social isolation and loneliness are one of the important contributors of stress in older adults. Some of the measures to prevent loneliness in older adults include keeping oneself occupied, helping others, developing relationships with people who share similar attitudes, interests and/or values, joining groups of self-interest/group activities. Others include training the older adults in using social media, and this in turn helps in connecting relatives/friends at distance. Visiting and participating religious activities also helps in preventing isolation (O'Rourke et al., 2018).

**e. Planning about late life in middle age**

With increase in life-expectancy more number of people live beyond 60 years of age. While people retire from usual work at 60 years, they are left with good 20 to 30 years of life to spend. Planning for late life in terms of their social security, place of stay and planning in terms of activities, hobbies, visiting places and philanthropic activities is essential. This will reduce the uncertainties and give meaning and purpose in their life for older adults.

**f. Promoting resilience in older adults**

Psychological resilience has been broadly defined as “the capacity to maintain, or regain, psychological well-being in the face of challenge (Ryff et al., 2012). Resilience depends on individual characteristics such as temperament and personality. In older adults, enhancing coping skills, healthy behaviours, social support and purpose of life are known to promote resilience. Older adults with higher resilience will cope with stress better and are at less risk of mental health issues (Sampedro-Piquero et al., 2018).

### **g. Promoting Age-friendly community**

World Health Organization (WHO) has recommended the promotion of Age-friendly community as an important requirement to promote healthy ageing. Promoting age-friendly physical and social environment, transport systems, health systems, respect and social inclusion are some of the recommended measures that can reduce stress for older adults and promote healthy ageing.

## **CONCLUSIONS**

Ageing is associated with many challenges and increased exposure to stress. Many older adults develop physical and mental health issues related to stress. This can have significant adverse impact on the mental health and well-being of older adults. However, many older adults are also resilient and manage these stress effectively to achieve successful and healthy ageing. There is evidence to suggest that older adults can develop resilience, coping skills and improve their adaptation to stressful conditions. There is a need for collective efforts from the family, society and the Government to provide required support systems that can help older adults to minimize the stress and promote well-being.

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## **OCCUPATIONAL STRESS**

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OUTLINE	
1. INTRODUCTION	2. DEFINITION
3. EPIDEMIOLOGY	4. THEORIES OF OCCUPATIONAL STRESS
5. ASSESSMENT OF STRESS AND DISABILITY	6. EPIDEMIOLOGY
7. PREVENTION STRATEGIES IN OCCUPATIONAL STRESS	8. RISK FACTORS OF OCCUPATIONAL STRESS
9. PROGNOSIS	10. INTERVENTIONS FOR OCCUPATIONAL STRESS

### **INTRODUCTION**

*Occupational stress* was a term originally used to define chronic ongoing stress related to the workplace. This term is now used in a much wider sense. The widely publicized studies on stressful deployments of military personnel and incidental accidents in a variety of situations are increasingly being considered as occupational stress resulting in psychological injuries in addition to physical injuries (Akanji, 2013). This is in sharp contrast to previous definitions of injury related only to physical harm. The stress may have its origin from a wide range of possibilities. It may have to do with the responsibilities associated with the work itself or be caused by conditions that are associated with peer pressure or in executive positions it could have its origin from the corporate culture or personality conflicts(Dewe et al., 2012). In all situations however, an interplay of various environmental, physical, psychological and social factors has an etiological, maintaining and therapeutic role.

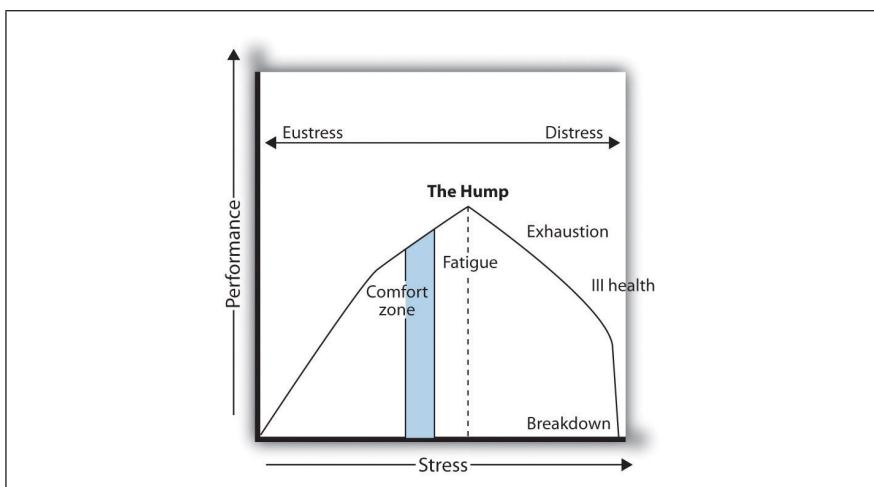
Occupational stress also implies ongoing stress that is related to the workplace. The stress may be a result of various factors(Akanji, 2013). High job demands, longer working hours, time pressures, low job control, managerial bullying and conflicts with the organization are few of the important ones. As with other forms of stress, occupational stress can eventually affect both physical and emotional wellbeing if not managed effectively. It is heterogeneous in etiology, manifestation and consequently the strategies in prevention, screening and management vary too(Akanji, 2013). Interaction between occupational stress, life events and biopsychological factors can lead to an increased incidence of disability.

Stress is not necessarily an inherent factor in any type of vocation or career in most situations and often is a protective factor with good opportunities to lead an independent and healthy life though people under stress often seem to attribute such a relationship often. Premorbid traits and coping strategies have a role in its origin and subsequent outcome. Preventive steps including competency-based recruitment and a culture of supportive continuing professional education and training have been the response from employment organizations and management professionals. Unfortunately, their primary aim seems to be prioritized productivity of employment organizations and reducing errors in high precision maneuvers like medical procedures (Dewe et al., 2012) and aero plane pilots. These protocols focus on openness and reducing blame on personnel and looking at organizational deficits in reducing errors of individuals (Blame in organizations - Wikipedia, 2020). Using such strategies has been an increasingly recognized inherent organizational process in addressing these factors related to stress and reducing individual stress in high risk professions.

Labor laws and policies for stress and sickness have been reformed (International Labour Organization, 2020) and empowered people perceiving stress to address it along with easy access to treatment and rehabilitative services. It is not essentially a good way to formulate that ‘Stress at its best can be a motivator that urges the individual to strive for excellence’. Stress however necessarily need not automatically lead to a lack of productivity, a loss of confidence, and cause inability to perform routine tasks. This holds true especially if an organization can introduce the right way of training individuals to promote learning and teamwork. However, as a result of stress, quality employees continually lose their enthusiasm for their work. This may eventually stop people from working along with persisting risks which can be enduring) (Blewett et al., 2006).

Stress is not necessarily an inherent factor in any type of vocation or career. In fact, some amount of stress is essential to motivate an individual to productively work through challenging situations and tasks. This is called *eustress* (*Eustress - Wikipedia*, 2020b). “Eu” comes from the Greek root word for “good”. As stress is inherently a reaction, the associated stressor has been cognitively appraised as positive or stimulating. Eustress is not defined by the stressor type, but rather by how it is perceived.

Figure 1: Eustress – Distress Vs Performance curve. Source: Adapted from P. Nixon, 1979



However, when a challenge is cognitively perceived to be a threat it causes negative stress or *distress*. This in turn leads to a lack of productivity and loss of confidence consequently affecting the ability to perform routine tasks (figure 1). Employees lose their enthusiasm for working when they are under an unpleasant pressure to perform. Distress can become crippling and lead to emotional turmoil and burnout. Organizational strategies such as teamwork instill confidence and are a deterrent against this stress.

*Prevention is better than cure* –so goes an old idiom. Competency based recruitment and ongoing continuing professional educational activities can prevent stress that arises from mismatched potential and job description. Unfortunately, their primary aim seems to be increasing productivity of the organizations while reducing errors

in fields that value high precision maneuvers such as medicine and aviation (Dewe et al., 2012). These protocols focus on openness, reduce blame on personnel and look at organizational deficits. Reformed labor laws and policies for stress and sickness have empowered people to address stress and access treatment and rehabilitation services.

The concept of workplace health surveillance is different from medical screening. Health screening refers to the early detection and treatment of diseases sometimes in the context of occupational health. Occupational health surveillance refers to the removal of the causative factors. The WHO Committee on Occupational Health has defined occupational health surveillance system as “a system which includes a functional capacity for data collection, analysis and dissemination linked to occupational health programmes (International Labour Organization, 2020). Various sources of stress include work environment, workload, isolation, shift hours and working hours, role conflict & ambiguity, lack of autonomy, difficult relationship with coworkers, harassment and organizational factors.

### **History of Occupational Stress**

The issue of occupational stress received attention by researchers from different perspectives because it affects both - individual employees and organizations. Occupational stress was not considered as a major concern till mid 1950's (Dewe et al., 2012) . Since then evidence suggests it to be a major health problem which has an impact on both physical and mental health. A survey done in England 1995 showed that about 500,000 people were suffering from work related problems like stress, depression and anxiety (Blewett et al., 2006). Life events and interaction of many other biopsychosocial factors leads to an increased incidence and disability of people who are affected by occupational stress.

The World Health Organization and the International Labor Organization have been focusing on Occupational stress and Health with local developments including legislations and implementing strategies at operational levels. These endeavors have been promoted by the Indian Government since Independence in 1947(International Labour Organization, 2020). Most of these welfare measures have been limited to Urban centers and rural employees have had very minimal support services. The reasons for such a lack of services have been investigated. These include

**Uneven growth:** Most large industries are concentrated in the metropolises, largely catering to organised sectors. Rural Agricultural labour and small-scale labour is grossly underrepresented. The vast majority of India's labour is not part of any trade unions. This reduces their collective bargaining power.

**Lack of public support:** Trade unionism is looked down as an impediment to growth and development. This has led to a general ebbing of the movement across the country.

## DEFINITION

Occupational stress has been defined in different ways during the past years based on etiological factors and disability variables. Those views vary between evaluating stress as a stimulus by itself or as physiological or psychological response to that stimulus. Alternative arguments focus on individual characteristics or as interaction between individual response to a situation or event. The functional consequence however seems to determine the term more appropriately in most circumstances. It refers to a factor causing discomfort and may extend to the point of decompensation to a disorder or injury. There are no specific disorders that are exclusive to the category of occupational stress. However various disorders and mental health issues can have occupational stress as part of a multifactorial etiology.

The National Institute for Occupational Safety and Health defines occupational stress as “the harmful physical and emotional responses that occur when the requirement of the job does not match the capabilities, resources or needs of the worker”(Smith et al., 2000). This definition mirrors the World Health Organization’s (WHO) definition- “Occupational or work-related stress is the response people may have when presented with work demands and pressures that are not matched to their knowledge and abilities and which challenge their ability to cope.” (World Health Organisation, 2020).

## EPIDEMIOLOGY

Labour in India refers to employment. There are 487 million workers in the country making India the second largest employer after China (Wikipedia, 2020c). More than two thirds work in unorganized enterprises which are not well paid (The Government of India, 2009). The workers are divided as organized sector workers which includes workers employed by the government, state-owned enterprises,

and private sector enterprises(Swaminathan, 1991; Ministry of labour and emploment, 2015). In 2008 the organized sector employed 27.5 million workers. The government contributed to two thirds of that number. Most of India's working population is part of the unorganized sector (The Government of India, 2009). Epidemiology with such a large unorganized sector is difficult to assess and there are no systematic large-scale studies to evaluate occupational stress.

India's Ministry of Labour, in its 2008 report, classified the unorganized labour in India into four groups based on occupation, nature of employment, specially distressed categories and services involved. The unorganised occupational groups include (Besley & Burgess, 2004).

1. First group comprises of small and marginal farmers.
2. Second group includes attached agricultural laborer's, migrant workers, contract and casual laborers.
3. Another category includes toddy tappers, scavengers, and carriers of head loads.
4. The last unorganized labor category includes service workers such as midwives, domestic workers, barbers and vegetable and fruit vendors.

Migrant skilled and unskilled laborers of India constitute about 40 to 85 percent of low wage working population in many parts of the Middle East. They are as much subjects of abuse and stress as the unorganized workers in India though the sociodemographic profile varies (9). The human rights record for these countries are very worrying. India has two broad groups of migrant labours - one that migrates to temporarily work overseas, and another that migrates domestically on a seasonal and work available basis (Wikipedia, 2020c).

#### **Legal labour laws:**

India has enacted numerous laws to help protect labor. These include:

1. Bonded Labor System Abolition Act (1976) to prohibit any and all forms of bonded labour practice, to protect the bonded labor, and to criminalize those who pursue bonded labour(Bhalla, 2003).
2. Article 24 of India's constitution prohibits child labor, but only in factories, mines or hazardous employment (Bhalla, 2003).

According to 2001 Census, India had 12.6 million children, aged 5–14, who work either part-time or full-time (Barman & Barman, 2014). Of these over 60 percent work in unorganized agriculture sector, and the rest in other unorganized labor markets. Poverty, lack of schools, poor education infrastructure and growth of unorganized economy are considered as the most important causes. A 2009–2010 nationwide survey found child labor prevalence had reduced to 4.98 million children (or less than 2% of children in 5–14 age group) (Swaminathan, 1991).

India also has other labor laws to prohibit discrimination, to guarantee fair and humane conditions of work, social security and minimum wage and to protect the right to organize and form trade unions.

Indian labor laws are very highly regulated and rigid. The rigidity of these laws have contributed to low employment growth, large unorganized sectors, underground economy and low per capita income (Bhattacharjea, 2006).

#### **Specific laws for occupational disability**

1. Workmen's Compensation Act of 1923 (Lazarus & Folkman, 1984) compensates workmen for any injury suffered during their employment or to their dependents in the case of his death.
2. Industrial Employment (Standing orders) Act of 1946 (Lazarus & Folkman, 1984) promotes employers in industrial establishments to define and post the conditions of employment approved by the government.
3. Industrial Disputes Act of 1947 (Lazarus & Folkman, 1984) regulates how employers may address industrial disputes and lawful processes for reconciliation, adjudication of labor disputes.

**Table 1: Relative regulations and rigidity in labor laws- International comparison**  
(Andrews, Baker and Hunt, 2011)

Country wise minimum standards	India	China	The USA
Minimum wage (US\$/month)	45(INR 2500)	182.5	1242.6
Standard workday (hrs)	9	8	8
Minimum rest while at work	30 mins per 5-hrs	None	None

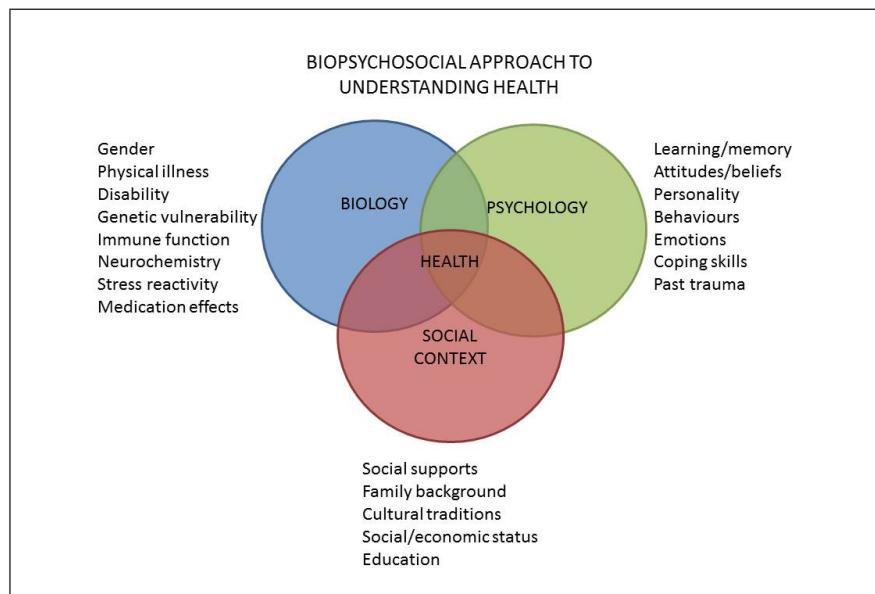
## THEORIES OF OCCUPATIONAL STRESS

Theoretical framework for occupational stress does not come up with any specific theories different from other stresses.

A **stress appraisal – coping transactional theory model** by Lazarus & Folkman (1984) describes the relationship between the individual environment as a dynamic, reciprocal and bidirectional. This model explains how individuals react to environmental changes based on their appraisal of certain situations. The reactions include physiological, psychological and behavioral response. This model includes two major processes, the first one is a cognitive appraisal which evaluates the situation, and the second process is the response to that stressful situation and how the individual manages that demand.

Another theory is the **Person–Environment fit theory** (Leigh *et al.*, 1999) which explains the effect of work stress on individual based on two dimensions. The first one is the balance between individual's expectations about work and what exactly the individual receives from it. The second dimension is the balance between individual's capabilities and the workload (Mohan & Patel, 1992).

**Figure 2: Biopsychosocial approach to understanding health**



Fit model is relatively comprehensive and put emphasis on the individual's subjective interaction with the environment. Other models focus on interactions with the work environment to understand the stress response. For healthy conditions, it is necessary that employees' attitudes, skills, abilities and resources match the demands of their job, and that work environments should meet, workers' needs, knowledge, and skills potential. Lack of fit can relate to health-related issues.

**Job model** focuses on the important aspects of job characteristics, such as skill variety, task identity, task significance, autonomy, and feedback which lead to experienced meaningfulness, and experienced responsibility and knowledge of outcomes.

Job demand resource model assumes that stress is a response to imbalance between demands of one's job and the resources to deal with those demands.

Effort reward imbalance model (ERI). The model focuses on the reciprocal relationship between efforts and rewards at work.

None of these models are comprehensive, the effects of stress on the individual and the organization, and methods that may control, or alleviate stress in the work setting are very variable though some professions do have higher risk.

## ASSESSMENT OF STRESS AND DISABILITY

There have been several approaches to address assessment of stress and resulting disability. The association with remediation, with a need for a livelihood through continued work and occasional association with compensation, complicates the assessment process. Even professionals who consider themselves to be objective and very good judges of character, frequently get it wrong. The correct approach to assessment of fact is to compare and contrast what is being said to professionals with all the other available information and to identify its consistency or inconsistency with the information which a employee provides or is provided on his behalf by employer and clinical professionals.

In the context of incapacity benefits associated with disability three main features can indicate the likely disability level:

1. Clinical findings
2. Available description of an employee's functional ability and

### 3. Underlying nature of an appellant's illness or disability.

Although clinical assessment forms the basis of assessment of disability, decisions are frequently contested and reviewing psychosocial situation of the employees to prioritize patient needs is helpful in relation to any questions which require to be asked. Another factor which might be worth considering, is that many employees, particularly those with mental health issues may find the assessments stressful. The lengthier and more prolonged the questioning, the more stress professionals subject them to. Focusing closely on what we need to know (as opposed to what we would like to know) will be a useful way of functional assessment.

### **Method of Questioning**

Many medicolegal practitioners operate in what is known as the “adversarial system”. This means that we start from a prepared position. Occupational health assessment is done for various purposes. The preventive aspects of occupational health are part of public health endeavors in an organization. However, when some critical incidents happen a proactive approach is advised to prevent consequential complications and to enhance recovery. The general clinical encounters of a general hospital are often replicated in such consultations. However, some specific interventions depend on specific occupations.

A separate group of people with residual symptoms often need assessment for remedial interventions or compensation. In these situations, the questions which the practitioner will ask are often designed to establish and support that prepared position. The extent to which such questioning will be successful depends upon many things. However, the objective is always to be professional and work in the patient’s best interests.

Contested decisions often end up in Tribunals. In evaluating disability in Tribunals, the situation is radically different. Medical professionals do not have any position to establish or support and are part of a judging panel supported by a tribunal judge. Tribunals operate in what is known as an “inquisitorial system”. This means that employment tribunals are genuinely asking questions with the sole purpose of obtaining factual information to help make a decision. The factual information which will enable a reasoned conclusion in relation to the resolution of any conflict in the evidence before the tribunal.

### Some Dos

- **Simplify the questions:** Keep questions simple and uncomplicated. This will help clinicians to frame an appropriate question. It will also help the stressed employee to understand the question and therefore to answer it.
- **Rephrase or repeat:** If an employee provides an answer which is incomplete or fails to address the question, ask a supplementary question or bring them back to the point in a simple and uncomplicated way. If necessary, reframe the question in a language and accent they can understand.
- **Listen well:** Pay careful attention to the answer which an employee provides. It is just as important to be a good listener as it is to be a good questioner. It helps reassure the employee in an adverse situation.
- **Seek and provide clarifications:** Open questions are ideal but where necessary, following up any relevant information which an employee provides in answer to a question with another simple understandable question designed to clarify the issue or resolve any potential ambiguity. It is important to address any difficulty which an employee has and provide clarification where appropriate.
- **Use open questions:** Why do you do that? Who does that? What do you cook? Which one do you use?

**Use appropriate body language:** Make sure that an employee understands that you are genuinely interested in hearing what they have to say

- Explore further: Remember that where you require some form of explanation, the interrogative “why” can be extremely useful.

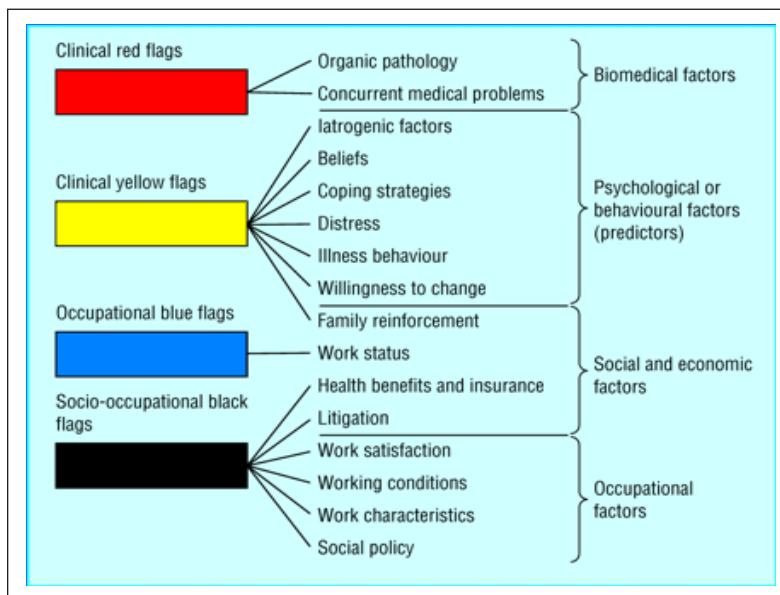
It is seldom, if ever, necessary to confront an employee with evidence which contradicts their own stated position. However, it may be entirely necessary to achieve a fair hearing in a tribunal, to refer an employee to such evidence for their comment. It is a very straightforward matter to do this in a simple and non-confrontational way. The objective is simply to afford the employee an opportunity of providing any explanation which he wishes to give. That explanation can then properly be considered along with all the other evidence available.

**Some Don'ts**

- Avoid complicated questions. Even more importantly, avoid asking questions which address more than one issue. Such questions are seldom, if ever, necessary. They will confuse the patients. Do not interrupt a patient unless necessary. Interruption may be necessary where an employee has clearly misunderstood the nature of the question or is providing an answer which does not address the question at all. Where such interruption is necessary, do so politely and bring the employee back to the question as quickly and as appropriately as you can.
- Do not be too inflexible. It is not always necessary or even appropriate to stick to this rigidly at the hearing.
- Avoid commenting upon the evidence. Such comment is often well-intentioned. However, it is frequently misinterpreted by patients and may, correctly or incorrectly, lead an employee to the view that you have formed some conclusion in relation to the evidence about that matter. Some discretion may be appropriate here. It is perfectly proper and indeed may be quite necessary to say something to an appellant who is clearly upset, anxious or distressed. However, such remarks do not require to directly refer to any evidence which is before the Tribunal and it is wise to ensure that they do not. This statement especially applies to Tribunals with an adversarial system of hearing.

Challenging an employee's position is inappropriate. Such conduct will usually provoke an adverse response which is unlikely to assist in a physician's primary duty. It may contravene the rules governing a fair hearing, .will heighten any perception on the part of the employee that the interviewer has come to some form of conclusion and is generally unhelpful

Figure 3: Physical evaluation needs to address these variables



## Epidemiology

Approximately 10 million people were employed in various factories. The current burden of accumulated occupational diseases in India is estimated to be at around 18 million cases (Mohan & Patel, 1992). The annual incidence of occupational disease is between 9-19 lakhs. Around 1.2 lakh deaths are attributable to occupational disease in Northern India, an annual incidence of 17 million injuries per year, with 2 million injuries being moderate to serious and 53,000 deaths per year in agriculture sector alone was reported (Jacoba & Sebastiaan, 2009). In India the traditional public health concerns like communicable diseases, malnutrition, poor environmental sanitation and reproductive health care get emphasis and priorities in the health policy. The major occupational diseases/ morbidity of concern in India are silicosis, musculoskeletal injuries, coal workers' pneumoconiosis, chronic obstructive lung diseases, asbestosis, byssinosis, pesticide poisoning and noise-induced hearing loss.

Census figures (2001) reveals an increase of about 28% male workers and 45% female workers from 1991 to 2001. The male: female working population ratio of 78:22 in 1991, has changed to 68:32 in 2001. Female workers have specific stress related disorders, resulting from job discrimination, increased demands on their

dual roles and issues around sexual harassment. Despite the existence of law that prohibit a paid work from children under age 14 years, an estimated 70-115 million children are part of Indian work force.

Byssinosis was first recorded in Indian history of 150 years textile industry. It continues to be a problem in the Textile industry. Compared to factories, mining industry has a much higher proportion of fatal and nonfatal injuries. However, agriculture still forms most occupational injuries. Some mine disasters in India have demonstrated the perpetual difficulties in the planning for disaster management. Chasnala Mines Disaster in 1975 was one of the worst disasters with 431 deaths. First aid and emergency treatment continue to pose a big challenge(Mohan & Patel, 1992).

In India, occupational health is not integrated with primary health care. Occupational Safety and Health is under the Ministry of Labour. Ministry of Health has a limited role. Enforcement of occupational health is by the Directorate of Industrial Safety and Health at state levels. They are implemented through factory inspecting engineers and medical inspectors of factories.

The Employees' State Insurance Corporation [ESIC] provides an integrated health care and Occupational health care to 80 lakh employees. It has Occupational Diseases Centers to provide early detection and diagnosis of occupational diseases among ESI beneficiaries. It was set up in the year 1952 under the ESI Act 1948. It is a workers' and employers' contribution-based health insurance corporation. The corporation has been audited by the apex audit institution of India, the Comptroller and Auditors General of India in its report for the year 1995 and the year 2005 pointing large scale deficiencies in the functioning of the corporation. Occupational Health Centers are mandatory at various hazardous process factories or units and a full-time occupational health physician is required when the number of employees exceeds 200.

There are around 1125 qualified occupational health professionals in India and only around 100 qualified hygienists as against a requirement of over 10000 qualified occupational health doctors. Occupational Health Institutes in India provide training and research in occupational health. These include

1. Central Labor Institute (CLI), Mumbai
2. National Institute of Occupational Health (NIOH), Ahmadabad
3. Industrial Toxicology Research Centre (ITRC), Lucknow
4. Central Mining Research Station, Dhanbad
5. Regional Occupational Health Centers at Calcutta and Bangalore
6. Regional Labor Institutes at Calcutta, Madras, Faridabad and Kanpur
7. Very few medical colleges and institutes

The Bhopal Gas Tragedy (4 December 1984) was a major landmark of our nation's deficiencies in health care and in providing justice and occupational health service including compensation. It undermined the political, judicial and medical inefficiencies with regard to occupational health. The Factories Act underwent a major revision in 1987 and practical implementation in the late 90s.

There are no systematic analysed data from India. Extrapolating data from other countries gives an idea of the level of stress and disability caused.

Figure 4: Trends in disability in the United Kingdom over time

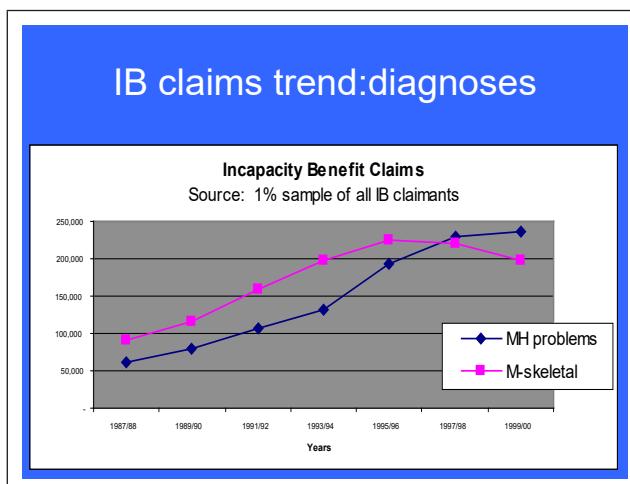


Figure 5: Deaths based on Diagnosis in 2001 (UK Statistics)

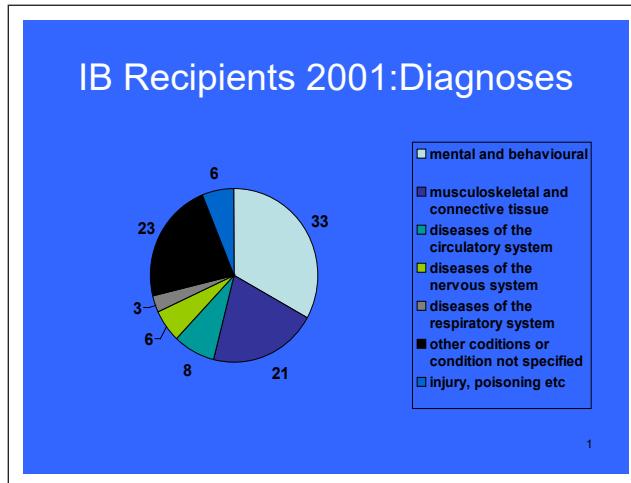
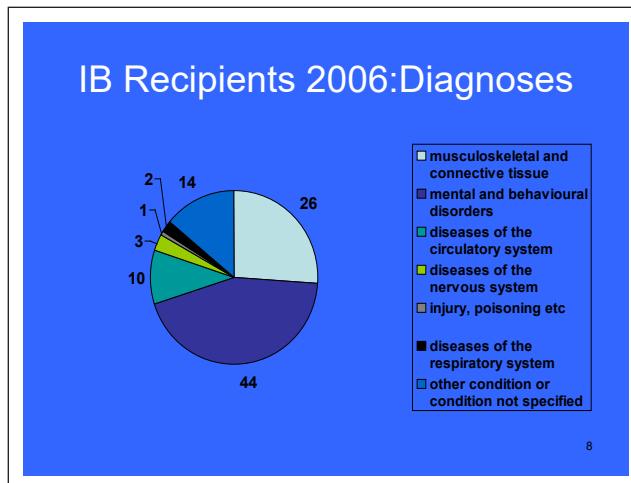


Figure 6: Change in disability diagnosis in 2006 (UK Statistics)



## PREVENTION STRATEGIES IN OCCUPATIONAL STRESS

The World Health Organisation has remained a pioneer in strategies to prevent stress and promote occupational health. The Sixtieth World Health Assembly considered the draft global plan of action on workers' health (Katherine and R, 2008). The global strategy aims for occupational health for all. It has linked it to

public health; Population health approaches act upon a broad range of factors that affect health including:

- a) Income and social status;
- b) Social support networks;
- c) Education;
- d) Employment and working conditions;
- e) Physical environment;
- f) Biology and genetic endowment;
- g) Personal health practices and coping skills;
- h) Healthy child development; and
- i) Health services.

The workplace, although a sector of the entire population, is in fact, a small community. The workplace itself, along with its health and safety initiatives, is the center of a community's socioeconomic capability. Health promotion may be thought of as all activities that enable and facilitate health within a primary health care framework. It considers that the health of workers is determined not only by occupational hazards, but also by social and individual factors, and access to health services. A major resource is reliance on primary prevention of occupational hazards and for developing healthy workplaces. There are major gaps between and within countries in the exposure of workers and local communities to occupational hazards and in availability and access to occupational health services.

Need is a measurable health status deficit. It is a measurable opportunity to maintain or enhance health. Needs/impact-based planning is management strategy defined as program planning based on the identified needs and the ability of a population to benefit from strategies to meet those needs. Completing a needs assessment is part of the process of needs-based planning. Health of workers is essential for productivity and economic development and to be effective needs to be developed in collaboration with workers, employers and their organizations. In the 1970's, workplace health promotion programs started as an adjunct to occupational health and safety initiatives. Workers were encouraged to participate in programs

designed to encourage physical activity, healthy eating, and smoke-free living. The workplace was deemed to be an appropriate setting for delivering this behavior change messages as it has a captive audience and because the programs were generally well accepted by both unions and employers.

Measures to establish and strengthen human resource capabilities for dealing with the special health needs of working populations and to generate evidence on workers' health and effectively translate that evidence into policy and actions needs a dynamic system with leadership. Mental health services and surveillance mechanisms for human and environmental hazards and diseases introduced into local communities where mining, other industrial and agricultural activities have been set up is necessary and involves public health planning.

The early pioneering efforts in planning a city like Jamshedpur to meet the needs of employees have not been replicated though the possibility exists. Jamshedpur is the first planned industrial city of India, founded by Jamshedji Nusserwanji Tata. Jamshedpur has been selected as one of the cities for the Global Compact Cities Pilot Programme by United Nations, the only one to be selected in India as well as South Asia.

Occupational health systems need to have flexibility and resources to encourage development of comprehensive health and non-health strategies to ensure reintegration of sick and injured workers into work and society. Despite the availability of effective interventions to prevent occupational hazards large gaps exist.

Some essential common principles exist

1. All workers should be able to enjoy the highest attainable standard of physical and mental health and favorable working conditions.
2. The workplace should not be detrimental to health and wellbeing.
3. Primary prevention of occupational health hazards should be given priority.
4. Workplace can also serve as a setting for delivery of essential public-health interventions

## RISK FACTORS OF OCCUPATIONAL STRESS

Risk factors of occupational stress can be divided into two main groups:

1. factors relating to the organisation or work environment and
2. factors related to the individual himself.

### Organisational risk factors

The organisational structure and work climate may contribute to stress as follows-

- 1- Role conflict- This pertains to imbalance between job demand and expectation from the organization or from the supervisors (J Dewe et al, 2012) . Role conflict may also occur when there is imbalance between job requirements and requirements outside work. For instance, an employee may struggle to create a balance between work and home roles.
- 2- Role ambiguity- This arises when there is no clear job description to the person that can enable him to understand his duties and meet job expectations (J Dewe et al., 2012)
- 3- Level of responsibility-Certain jobs that need effective decision-making call for a high level of responsibility. These are likely to be more stressful than others,
- 4- Job type-Full time employment is more strenuous than part time. However, part time work carries its own unique stresses.
- 5- Hazardous occupations- Certain jobs are stressful by their nature such as firemen and miners.
- 6- Multifactorial causes: Job specific factors will influence levels of stress. To cite examples, physicians have long working hours, shift duties, high level of responsibility and possibility of litigations. These carry high level of responsibility which make the negative outcomes like depression and other mental problems as high concern among those staff.\_
- 7- The stressors among police personnel are usually related to their relationship with supervisors, long working hours, handling of risky situations and lack of reward.

### Individual risk factors:

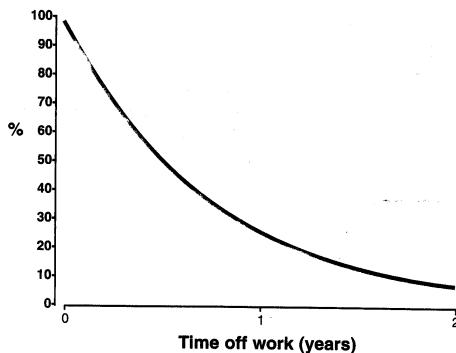
The second important factor is related to individual abilities such as coping strategies and personality. Leadership roles require specific personality traits and teamwork requires good social skills.

## PROGNOSIS

Outcomes of occupational stress related symptoms can be divided into three major categories: physiological, psychological and behavioral. Longer the period off work, lesser are the chances of returning to work (Figure 7).

Figure 7: Time off work Vs. Return to work

Figure 2 - Probability of return to work



Reference: Boorman, S. The Benefits of Managing Occupational Health & Well-being. Available at: <https://www.orr.gov.uk/sites/default/files/om/oh-event-abermed-071112.pdf> (Accessed: 31 October 2020).

## INTERVENTIONS FOR OCCUPATIONAL STRESS

Various modalities of management are applicable depending on individual needs. Specific interventions for physical health needs are usually quite clear and no different from other injuries sustained. However mental health needs and intervention needs some refinement.

Cognitive behavioural techniques, Relaxation techniques, organizational techniques, multimodal and other interventions have been used. Cognitive behavioural method is one of the most effective modalities. Relaxation techniques are most widely method to be used for management of occupational stress because of it is low cost and easy to perform. Some of organizational modalities for dealing with occupational stress are time management skills and job-related skills (Selokar et al., 2011). Management principles focus mainly on prevention. Secondary prevention techniques need further evaluation and evidence base for effectiveness in India is evolving

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## **STRESS AND DISASTER**

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### **OUTLINE**

- |   |                                |
|---|--------------------------------|
| 1. DEFINITION OF DISASTER                                     | 2. CLASSIFICATION OF DISASTER  |
| 3. EVOLUTION OF INTERNATIONAL DISASTER RISK REDUCTION EFFORTS | 4. TRAUMA FOLLOWING A DISASTER |
| 5. COMMON PSYCHIATRIC MANIFESTATIONS AND DISORDERS            | 6. MANAGEMENT                  |
| 7. FOSTERING RESILIENCE IN INDIVIDUALS AND COMMUNITIES:       | 8. CONCLUSIONS                 |

### **DEFINITION OF DISASTER**

The word disaster has been derived from Latin, where “dis” means “lack” or “ill” and “astrum” means “heavenly body” or “star”, hence, indicating bad luck or fortune (López-ibor et al., 2005). A disaster is an occurrence disrupting the normal conditions of existence and causing a level of suffering that exceeds the capacity of adjustment of the affected community (WHO, 2002). As per the United Nations Office for Disaster Risk Reduction (UNDRR), a disaster can be defined as a serious disruption of the functioning of a community or society at any scale due to hazardous events interacting with conditions of exposure, vulnerability and capacity, leading to one or more of the following: human, material, economic and environmental losses and impacts (UNDRR, 2020).

## CLASSIFICATION OF DISASTER

The disasters are divided broadly into two types: Natural and Man-made disasters.

### A. Natural Disasters:

Natural Disasters are naturally occurring physical phenomenon caused by rapid or slow onset events that can be:

1. Hydrological: Events caused by deviations in the normal water cycle. Example- floods, avalanches etc.
2. Geophysical: Geological phenomenon that can cause loss of life and property damage. Example- earthquakes, tsunami, volcanoes, landslides etc.
3. Climatological: Events occurring as a result of extreme variability in the climate. For example- draught, wild fires etc.
4. Meteorological: Events occurring as a result of extreme changes in the metereological processes. Example- Cyclones, storms etc.
5. Biological: Events caused by phenomenon of organic origin or through biological vectors. Example- infectious epidemics/ pandemics etc. (*National Disaster Management Plan National Disaster Management Authority Ministry of Home Affairs Government of India, 2019*)

### B. Man-made Disasters:

Man-made disasters are events that are caused by humans and occur in close to human settlements. For example: Environmental degradation, famine, industrial accidents etc. (International Federation of Red Cross and Red Crescent Societies, 2003).

The disasters can also be classified according to the intensity and the range of their impact, like demarcation of exposure, affected population, warning and impact of the disaster etc. (López-ibor et al., 2005), which serves as a better practical classification. Some common notable disasters across the globe in last few decades are:

- 2004- Indian ocean earthquake and tsunami
- 2008- Sichuan earthquake
- 2010- Haiti earthquake
- 2012- Hurricane Sandy

2014-2016- West African Ebola outbreak

2015- Nepal earthquake

2019- Global Wildfire

2020- Pandemic COVID-19

## **EVOLUTION OF INTERNATIONAL DISASTER RISK**

### **REDUCTION EFFORTS:**

Disaster risk reduction is the concept and practice of reducing disaster risks through systematic efforts to analyse and reduce the causal factors of disasters ('What is Disaster Risk Reduction? - UNISDR', n.d.). In order to implement this concept, an International Decade for Natural Disaster Reduction (IDNDR) was launched by the United Nations for the decade 1990-1999 began on January 1, 1990. The decade was intended to help the countries, especially developing to reduce loss of life, property damage and social and economic disruption caused by natural disasters, through a collaborative action (Hays, 1990). The first world conference on natural disaster reduction in Yokohama adopted the Yokohama strategy and plan of action for a safer world. It provided guidelines for natural disaster prevention, preparedness and mitigation (United Nations - Headquarters (UN), 1994). The IDNDR recognized that the disaster reduction was a socio-economic imperative that would take a long time to fulfil. As a result of this, the International Strategy for Disaster Reduction (ISDR) was adopted in 1999 in Geneva. The aim of the strategy was basically to proceed one step ahead of enhancing awareness, assessment and management of risk of the disasters ('International Strategy for Disaster Reduction (ISDR)', 2006).

Following this, Hyogo framework for Action (2005-2015) was adopted which aimed to build resilience of nations and communities to disasters. The conference provided an opportunity to promote a strategic and systematic approach to reduce vulnerability and risk to hazards (Nations, 2005). The Sendai Framework for Disaster Risk Reduction 2015-2030 was adopted at the third UN World Conference in Sendai, Japan, on March, 2015. It was a successor instrument to the Hyogo framework for action. The aims were to achieve substantial reduction of disaster risk and losses over the next 15 years and outlines priorities for action to prevent new and reduce existing disaster risks ('Sendai framework for disaster risk reduction 2015-2030', 2015).

*“The more governments, UN agencies, organizations, businesses and civil society understand risk and vulnerability, the better equipped they will be to mitigate disasters when they strike and save more lives.”*

*- Ban Ki-moon, United Nations Secretary-General*

## **TRAUMA FOLLOWING A DISASTER:**

Majority of the people who are exposed to the disasters do well, as the survivors are normal people in abnormal situation (Math et al., 2015). However, some of these individuals develop distress, some develop normal grief reactions that resolves over a period of few months and some develop psychiatric disorders after the disaster. The reaction to the trauma or disasters depends on multiple factors like type of disasters, duration of trauma, disruption to individual and community life, personality factors of the individual itself that we will discuss in further sections.

### **Factors affecting the reaction to the trauma or disasters:**

#### **A. Disasters related factors:**

- a. **Nature and severity of the disasters:** The nature and severity of the disasters will influence the psychological or behavioural reactions of its survivors. The higher the intensity and the duration of the exposure of the disaster is, the higher is the psychological impact on the affected individuals (Frankenberg et al., 2008).

Natural disasters affect many people, cover a wide area and last a significant length of time; however, the man-made disasters are usually limited in time and space, but the possibility of recurrence may leave the survivors insecure (López-ibor et al., 2005).

#### **B. Individual related factors:**

- a. **Age:** It is studied that young and older adults are more vulnerable to the affect of the disasters as the young people may have multiple financial burdens and responsibilities and older adults may find it difficult to reconstruct the losses due to their old age. Other high-risk group includes children, elderly, women etc. (López-ibor et al., 2005).
- b. **Socioeconomic demographics:** Factors like lower socioeconomic status, single, ethnic minority, displaced population, poor social support and family support are some of the factors responsible for developing mental

health morbidity (Bhugra & Ommeren, 2006) (Bhugra & Ommeren, 2006).

- c. **Past history of psychological symptoms:** It is studied that the previous history of the psychological symptoms is one of the best predictor of post-disaster psychiatric morbidity (Norris et al., 2002).

**C. Other factors:**

- a. **Predisposing factors:** The psychiatric disorders and physical symptoms are found to be more frequently diagnosed in females than males. The few reasons could be that females are at high risk of intimate partner violence, physical and sexual assault after the disaster and carries a heightened responsibility of managing the distress and emotional turmoil in family. Pre-trauma functioning is also an important determinant in understanding the level of functional impairment. Individuals functioning marginally in socio-occupational roles and having history of childhood abuse and significant trauma in past are among the high risk of developing psychiatric comorbidities post disaster.
- b. **Precipitating factors:** The intensity and duration of exposure of disaster increases the likelihood of psychiatric problems. Specific experiences like witnessing deaths, torture, physical injury, victimisation of any kind also precipitate significant distress.
- c. **Protective factors:** Loyalty, interpersonal cohesion among members of organization and strong leadership are few of the factors that are found to be protective that may diminish the potential consequences of trauma. Also, absence of risk factors such as past psychiatric history, resilience, good social support is also studied to be as protective factors.

## **COMMON PSYCHIATRIC MANIFESTATIONS AND DISORDERS:**

Common psychiatric manifestations that can be seen during disasters are (Math et al., 2015):

- Anger and irritability
- Fear

- Restlessness
- Sadness
- Insomnia
- Somatic complaints
- Concentration difficulties
- Increase in substance use

Common Psychiatric Disorders seen are:

- a. Acute Stress Reaction
- b. Post-Traumatic Stress Disorder
- c. Generalised anxiety disorder
- d. Panic Disorder
- e. Major Depressive Disorder
- f. Psychosis
- g. Substance use disorder

#### **Details on Individual disorders:**

- a. **Post-Traumatic Stress Disorder (PTSD):** PTSD is a mental illness that can follow exposure to a disaster or a traumatic event. It is characterised by typical symptoms including episodes of repeated reliving of trauma in intrusive memories (flashbacks), occurring against a background of sense of numbness and emotional blunting, detachment, anhedonia and avoidance of activities or situations ('The ICD-10 Classification of Mental and Behavioural Disorders Clinical descriptions and diagnostic guidelines World Health Organization', 1990). PTSD is one of the most commonly occurring among post-disaster psychopathologies and is estimated to affect approximately 4 percent of the world's population (Koenen et al., 2017). Few factors that are associated with an increased risk of lifetime PTSD after the exposed trauma are women, less education, single, unemployed, young age, lower socioeconomic status (Koenen et al., 2017).
- b. **Major Depressive Disorder:** Major Depressive Disorder is also one of the most common psychiatric disorder post disaster. A systematic review and meta-analysis analysing the risk of depressive disorder in disaster survivors

and in soldiers returning from military deployment, the average odds ratio was significantly elevated in all type of exposures, i.e., 2.28 in natural disasters, 1.44 in technological disasters and 1.80 in terrorist attacks (Bonde et al., 2016).

- c. **Suicidality:** It is studied that the suicidality rates increases significantly post disaster. In a metanalysis done to understand the suicide death rates after the disaster, it was found that the suicide rates before and after the disasters were calculated as 13.61 (CI95%: 11.59–15.77) vs. 16.68 (CI95%: 14.5–19.0) among the whole population, 28.36 (CI 95%:11.29–45.43) vs. 32.17 (CI95%: 17.71–46.62) among men, and 12.71 (CI95%: 5.98–19.44) vs 12.69 (CI95%: 5.17–20.21) among women (Bonde et al., 2016). It is estimated that the new onset psychiatric disorders like PTSD and depression takes 2 and 4 weeks respectively to develop and be diagnosed. Hence, the assessments done during this time can address the distress effectively (Rugulies et al., 2016).
- d. **Substance Use Disorder:** Studies have found that disasters, regardless of type are found to have been associated with an increase in the prevalence of alcohol, tobacco and cannabis. Individuals with post disaster mental health problems are likely to use more substances than the individuals without any mental health problems (Forman-Hoffman et al., 2005) (Flory et al., 2009) (North et al., 2011) (Vlahov et al., 2004). The self-medication hypothesis is one of the theory that is frequently postulated in order to understand the use of substance post disaster (Vlahov et al., 2004).
- e. **Other Disorders:** Other disorders include adjustment disorders, acute stress reactions, anxiety disorders, abnormal grief, somatoform disorders, dissociative symptoms etc. (Math et al., 2015).

## **MANAGEMENT:**

The pharmacotherapy and psychotherapy are the standard treatments for psychiatric disorders related to disasters. The details are as follows:

### **A. Pharmacological Management:**

In the immediate or early post disaster phase, anxiolytics can be used to control the acutely disruptive behaviour. Short acting hypnotics can provide transient relief in sleep and anxiety symptoms during this time. Patients with pre-existing psychiatric problems will need medication refills to ensure continuity of care. Later during the

course of disaster, pharmacological agents like anti-depressants may be needed for the treatment of diagnosed PTSD and depressive disorders (North & Pfefferbaum, 2013). Anti-depressants like selective serotonin reuptake inhibitors are established treatment in the diagnosis of PTSD. Alpha 1 antagonist anti-hypertensive agent, Prazosin has been studied to alleviate symptoms of PTSD, especially trauma related night mares and sleep disturbances (Kung et al., 2012).

Other therapeutic agents like propranolol (beta adrenergic blocker), hydrocortisone (glucocorticoids), morphine (opioid agonist) have been studied to be effective in prevention of PTSD (Birur et al., 2017).

### B. Psychological Management:

The most common psychological interventions described are psychological first aid, psychological debriefing and crisis counselling. The details are as follows:

- **Psychological first aid:** Psychological first aid is the term used to describe practical early interventions and principles to address immediate post disaster distress. It can be used by clinicians or non-clinicians as well (Reyes & Elhai, 2004). Like the physical first aid, the goals are to stabilise functioning by meeting basic needs, addressing psychological needs, mitigating psychological distress, facilitating return to adaptive functioning and providing further access to care (Everly & Flynn, 2006).
- **Psychological debriefing:** Psychological debriefing is a group discussion that occurs within 24-72 hours after the traumatic event (S. B. Math et al., 2015). Its main elements are emotional ventilation, trauma processing and psychoeducation that aims at enhancing resilience of the individuals (North & Pfefferbaum, 2013).
- **Crisis counselling:** Crisis counselling is a brief, strength based mental health intervention usually done by trained and experienced crisis workers and professionals in acute disaster setting (Elrod et al., 2006).
- **Trauma focussed Cognitive Behavioral Therapy:** Trauma focussed CBT is a family focused treatment in which the parents participate with their traumatized children to enhance the family communication with regards to the child's traumatic experience and to support the child (Elrod et al., 2006).

- **Other interventions:** Other interventions like Eye Movement Desensitization and Reprocessing (EMDR) have been shown to be effective in PTSD (Seidler & Wagner, 2006). Exposure based therapies like cognitive processing therapy and virtual reality therapy have been investigated in disaster affected military populations (Seidler & Wagner, 2006).

## **FOSTERING RESILIENCE IN INDIVIDUALS AND COMMUNITIES:**

Community Resilience means “the ability of a system, community or society exposed to hazards to resist, absorb, accommodate to and recover from the effects of a hazard in a timely and efficient manner including through the preservation and restoration of its essential basic structures and functions” (Ostadtaghizadeh et al., 2015).

Resilience can usually be seen as an ongoing process of adapting to the changing environment, maintaining healthy levels of functioning and coping effectively and learning from the adversities (Patel et al., 2017).

### **Elements of community resilience have been studied which are as follows:**

Good local knowledge of the existing vulnerabilities by the community, understanding and addressing the vulnerabilities along with proper education and regular training, good social networks and social relationships between the communities, good communication networks, pre-disaster health of the people in the community, pre-existing resources, medical resources post disaster, effective governance and leadership, disaster preparedness at the level of individual, community, pre-existing mental health of the community dwellers and their coping strategies are some of the important elements in fostering community resilience (Patel et al., 2017).

## **CONCLUSIONS**

Disasters are either natural or manmade, occurring every year. Stress related to disasters are also commonly occur in affected population. There is a lack of systematic studies on disaster related psychiatric disorders in India. There is need for systematic studies on these areas.

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## **STRESS AND NEURODEVELOPMENTAL DISORDERS**

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### **OUTLINE**

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|--|---|
| <b>1. INTRODUCTION</b>   | <b>2. DEVELOPMENTAL DISORDERS AND VULNERABILITY TO STRESS</b>                               |
| <b>3. MANIFESTATIONS OF STRESS</b>   | <b>4. INTERVENTIONS FOR STRESS MANAGEMENT IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS</b> |
| REACTION IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS                       |   |
| <b>5. FOSTERING RESILIENCE IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS</b> | <b>6. CONCLUSIONS</b>   |

## **INTRODUCTION**

An actual or a perceived threat to an organism is referred to as a “stressor” (Schneiderman et al., 2005) and human beings evoke coping responses based on the appraisal of perceived threat (Lazarus & Folkman, 1984). Biological and behavioural stress responses include distressing emotions consisting of psychological, somatic, and behavioural manifestations (McCabe & Schneiderman, 1985). At optimal level reactions to psychological stress can be adaptive and protective in coping with adversity. However, stress response may be maladaptive depending on various factors - like type of stressor, frequency, intensity, subjective distress associated with the event and the individual coping resources and abilities (Calabrese, 2008). Individuals with developmental disabilities are not immune to the experience and consequences of stress, contrary to what was thought earlier. They are in

fact more vulnerable to experience stressful events than the general population and can respond in a maladaptive pattern that can be atypical and frequently go unrecognised. Stress can also have an impact on their developmental trajectory, lead to negative interactions with their caregivers and immediate environment leading to social isolation or institutionalisation (Cooper et al., 2007; Scott & Havercamp, 2014).

The focus of this chapter is on the vulnerability of children with Intellectual Disability (ID) to stress, atypical manifestation of stress reactions, challenges in making a diagnosis and ways to intervene in this subgroup of vulnerable population.

### **Neurodevelopmental Disorders – An Overview**

“Neurodevelopmental disorders” (NDD) were introduced as a comprehensive disorder category in the Diagnostic and Statistical Manual – fifth edition (DSM-5, American Psychiatric Association, 2013) and in the International Classification of Diseases-11 (ICD-11) published by the World Health Organisation (WHO). NDD include a wide spectrum of heterogeneous cognitive and behavioural disorders with a core feature of onset typically in the early developmental period, with impairment or delay in the development of functional abilities of brain. The disorders occur on a continuum of severity, tend to co-occur and have a continuous life course presentation across the lifespan. The range of developmental deficits varies from specific limitations in learning as in developmental learning disorder to global impairments in social skills or intelligence as seen in Autism Spectrum Disorder (ASD) and Intellectual Developmental Disorder (IDD) respectively (Maughan & Collishaw, 2015).

The term developmental disorders in this chapter is meant to include conditions with Intellectual Developmental Disorder [IDD]/ Intellectual Disability [ID] as a common feature. IDD includes a group of etiologically diverse heterogeneous conditions characterized by significantly below average intellectual functioning and adaptive behaviour that are approximately two or more standard deviations below the mean based on appropriately normed, individually administered standardized tests(ICD-11 - WHO ; Stein et al., 2020). Intellectual functions include cognitive abilities such as perceptual reasoning, working memory, processing speed, and verbal comprehension. Adaptive functions are defined in terms of conceptual, social, and practical skills involving tasks performed by people in their everyday lives.

## DEVELOPMENTAL DISORDERS AND VULNERABILITY TO STRESS

One of the major determinants of mental health problems in the general population is the experience of stress. An individual experiences effects of stress when a particular event is perceived as overly challenging and beyond one's coping abilities (Chan, 1977; McCabe & Schneiderman, 1985). The earlier belief that individuals with IDD lack the cognitive capacity to get adversely affected by stress is being refuted now (Bradley et al., 2012; Scott & Havercamp, 2014). Various community and hospital-based studies have conclusively proven that children with IDD are more vulnerable to stress than the general population and are at higher risk of developing comorbid psychiatric disorders. Several community-based studies have reported the prevalence of diagnosable psychiatric disorders in children and adolescents with ID to be around 35 to 40% (Hemmings & Bouras, 2016 ; Einfeld & Tonge, 1996; Einfeld et al., 2006; Einfeld et al., 2011).

Children People with ID experience the same stressful major life events as the general population with significant life events being one of the major triggers of emotional and behavioural crisis in the ID population (Hastings et al., 2004; Hulbert-Williams & Hastings, 2008; Bond et al., 2019). Crisis often follows death of a parent or major care giver particularly when no plans are in place or following major trauma like abuse or serious injury.

They can perceive stress not only due to major life events but also because of minor and daily life activities due to their limited adaptive functions, coping abilities, socio-emotional and communication difficulties, which make them more dependent on support system (Ghaziuddin, Alessi & Greden, 1995; Hulbert-Williams & Hastings, 2008). Thus, they become more vulnerable to cope with day-to-day activities like social and peer group interactions, completing academic tasks, independent living, adapting to change in caregiver or residence. Studies have revealed that certain common forms of stress are reported more common in people with ID – such as hearing people argue, death of or serious illness in an acquaintance, constantly being interrupted and interpersonal communication difficulty (Alvord & Grados, 2005). These difficulties in overcoming their routine often creates a sense of low self-esteem with poor sense of self-identity. Over the age, older adults with ID are significantly more likely to receive less emotional support from others than individuals without disabilities (Scott & Havercamp,

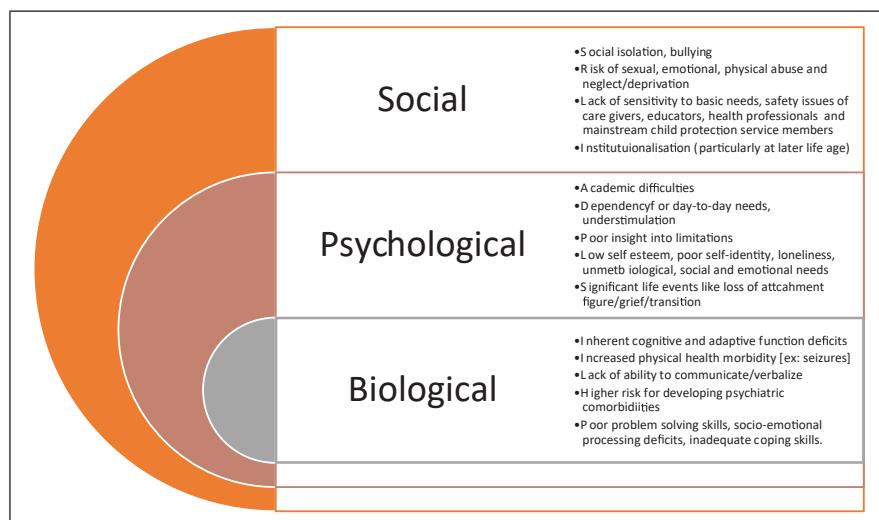
2014). This could be due to loss of the primary caregiver. This would result in feelings of loneliness that are worsened by their placement in long term residential setting or paid care services (Lunsky, 2008).

Moreover, they are at high risk of being a victim of bullying, emotional, sexual, and physical abuse including neglect because of their dependency on others, limited awareness on concept of safety and protection, and ability to conceptualise and express their distress (Sequeria & Hollins, 2003; Esbensen & Benson, 2006; Evans et al., 2013).

The subjective experience of adults with ID has been given very little importance. A study focussing on the same found that caregivers of children with ID were not always aware of latter's perceived stressors and focused more on their inadequacies and deficits than did individuals with disability themselves (Lunsky & Bramston, 2006; Hartley & MacLean, 2009). Their motivation, desire to learn, need for peer group interactions and emotional support were given less significance.

Figure 1 represents a biopsychosocial and ecological framework that explains the vulnerability of individuals with IDD to stress – due to a combination of factors either within the individual or in their immediate surroundings and the community.

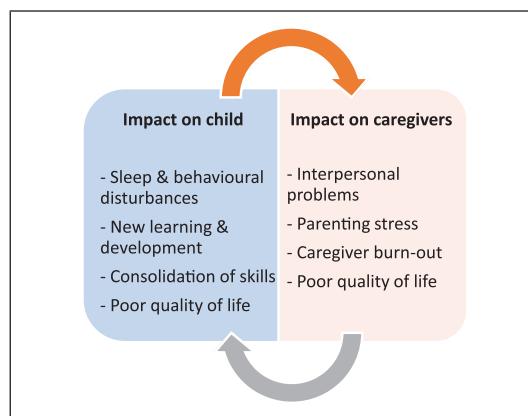
**Figure 1: Biopsychosocial and ecological framework**



### Impact Of Stress In Developmental Disorders

Stress can have short-term and long-term impact. In the short-term, it can lead to sleep and behavioural disturbances. Stress is also known to have an effect on learning and motivation (Lindau *et al.*, 2016). Hence, it can cause impairment in new learning and consolidation of skills that in turn adversely impact the developmental trajectory. It is important to note that it affects not only the child but also caregivers. Caregivers of children with developmental disabilities face challenges due to social isolation, lack of community understanding and child's unpredictable behaviours, inability to communicate or care for self (Almogbel *et al.*, 2017; Craig *et al.*, 2016; Ludlow *et al.*, 2012; Nik Adib *et al.*, 2019). In addition, new-onset problems due to stress can further exacerbate parenting stress, lead to interpersonal problems and caregiver burn-out. Therefore, the importance of social support for caregivers cannot be underemphasized. Impact on child and caregiver can be inter-related as depicted in figure 2.

Figure 2: Impact of stress



## MANIFESTATIONS OF STRESS REACTION IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS

Children with IDD react to stress and adversity in different ways. Psychopathology can be manifesting in the form of

- 1] Challenging behaviours like self-injurious behaviour, disruptive behaviour which can be either a new onset behaviour or worsening of pre-existing behaviour (Einfeld & Tonge, 1996; Einfeld *et al.*, 2006)
- 2] Emotional and behavioural problems with or without a diagnosable psychiatric

disorder (Esbensen & Benson, 2006; Matson & Matson, 2007; Einfeld et al., 2006; Munir, 2009)

### **Challenges In Diagnosis Of Stress Reactions And Psychopathology**

Compared with neurotypical population, individuals with IDD have a significant impairment in cognitive processing and verbal communication to be able to understand and communicate the adverse experience. (Cooper et al, 2007; Costello & Bouras, 2006; Girimaji & Pradeep, 2018). This leads to diagnostic masking as expression of distress is essential for identification of underlying distress or psychiatric disorder based on the standard ICD/DSM criteria. The presentation can also be in the form of baseline exaggeration in intensity and frequency of pre-existing maladaptive behaviours.

In children with mild to moderate ID the reaction to stress can be diagnosed with modification of existing criteria. However, in those with severe and profound ID who usually show distinct pattern of symptoms and aberrant behaviours, it will be challenging to rely on the standard clinical interview or classificatory systems that are less sensitive to personal developmental level, cultural and other social factors (de Ruiter et al., 2007).

The other major challenge is the ‘Diagnostic Overshadowing’ wherein debilitating problems signifying psychopathology are given less significance when they occur in the context of intellectual disability. The symptoms are dismissed by attributing it to the level of ID by both mental health professionals and the care giver (Reiss et al , 1982). This lead to the concept of ‘Behavioural Equivalents’ that denote the observable behaviour seen in individuals with ID. In the context of their cognitive abilities, which may indicate diagnostic equivalents to essential criteria required for the diagnosis of psychiatric disorders or a pathological reaction to ongoing stressors ( Langlois & Martin, 2008). In addition to the above challenges, poor understanding of developmental psychopathology makes diagnosis difficult in children and adolescents (Jones et al., 2008; Bond et al., 2019). Therefore, assessment and diagnosis of psychopathology in this subgroup should be exercised with caution by judging the symptoms in the context of developmental delay. Information should be collected from multiple informants and a careful observation should be made to assess for any change in observable behaviour or new-onset signs – that can be an equivalent symptom criterion signifying an underlying distress or disorder.

Table 1 summarizes certain equivalent behaviour/manifestations of trauma and stress related disorders in individuals with IDD.

**Table 1: Behavioural Equivalents**

Acute stress reaction and Adjustment disorders	<ul style="list-style-type: none"> <li>• Avoidance</li> <li>• State of daze (equivalent to dissociative symptom), avoidance of eye contact</li> <li>• Physical health problems</li> <li>• Disturbance in biological functions like sleep and appetite</li> <li>• Confusion, wandering behavior.</li> <li>• Specifically, in children and adolescents – clinging behavior, irritability, tantrums, withdrawn, overexcitement, resistance to change, disturbance in biological functions, soils/urinates in dress</li> </ul>
Post-Traumatic Stress Disorder [PTSD] (Hartley & MacLean, 2009b) (Breslau et al., 2013)(Denton et al., 2017)	<ul style="list-style-type: none"> <li>• Frightening dreams without recognizable content [in severe/profound ID]</li> <li>• Avoidance behavior with limited participation presenting as oppositionality</li> <li>• Avoiding physical contact</li> <li>• Behavioural acting out in the form of agitation or self-injurious behavior (signifying hyperarousal symptoms)</li> <li>• Regression in daily living skills.</li> <li>• Symptoms like depersonalisation, derealisation, dissociation are uncommon.</li> </ul>
Symptoms of depression and anxiety (Tsiouris, 2001; Bridge et al., 2005; Hurley, 2006, 2008)	<ul style="list-style-type: none"> <li>• Depressed mood described by the caregivers as mood drift from being happy/smiling/laughing to the absence of them, tearfulness</li> <li>• Apathy and refusal to participate in routine activities (anhedonia)</li> <li>• Pacing, inability to sit still, general restlessness (agitation)</li> <li>• New onset or worsening of pre-existing self- injurious behaviour, stereotypes, running away, aggression (agitation).</li> <li>• Increase in somatic complaints and irritability, weight loss, food refusal.</li> <li>• Trouble in completing the activities of daily living, regression of skills (loss of energy)</li> <li>• Making statements such as "Nobody likes me", "I can't do this job" (feelings of worthlessness or excessive inappropriate guilt)</li> <li>• Beginning a task but not completing it (decreased concentration).</li> <li>• Deliberate lethal acts or self-injurious behaviour, expressing verbally – "I want to go away" or "be with grandmother who died" (suicidal ideation).</li> </ul>

**Death, Bereavement and Grief:** One of the major stressors as mentioned earlier is the loss or death of loved ones. In the past it was considered that children with ID are not able to experience grief reactions. Individuals with ID have limited understanding of the concept of death including its causality, finality, and universality due to their cognitive limitations (Hastings et al., 2004; McEvoy et al., 2002; Speece & Brent, 1984). The initial bereavement reaction can be – increase in irritability, lethargy, inappropriate speech, anxiety, confusion. Prolonged grief reaction in general can be manifesting as symptoms of separation distress (Brickell & Munir, 2008; Dodd & Guerin, 2009). Attachment difficulties are central to loss experience leading to prolonged grief reaction manifesting as separation distress symptoms such as longing and searching for deceased, and even depression given the centrality of the life event. Other possible reactions are – loneliness, preoccupation, anger, shock, confusion, detachment from others than traumatic symptoms like disbelief, feeling of emptiness, guilt, bitterness, avoidance of reminders and hopelessness (Dodd et al., 2008; Guerin et al., 2009).

It is worthwhile noting that due to cognitive limitations in understanding the meaning of loss and communication difficulties, children with ID are vulnerable to develop pathologic grief reactions to secondary losses such as loss of home or even moving to a residential setting (Dodd et al., 2005; Dodd *et al.*, 2008).

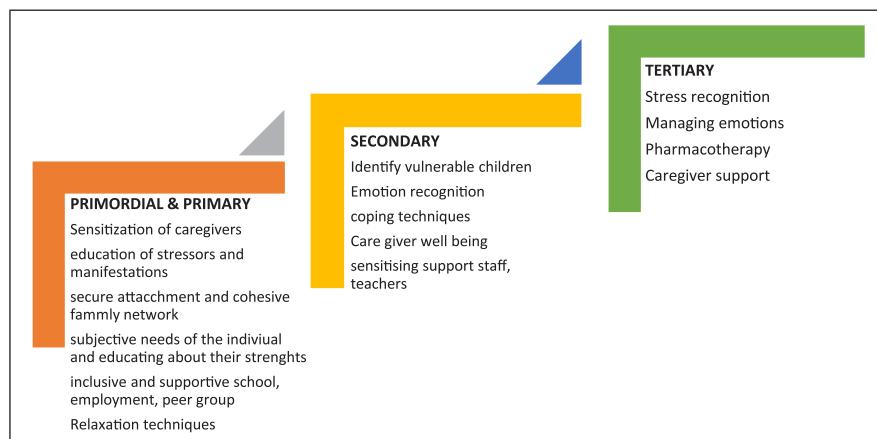
**Developmental disabilities and sexual abuse:** Disabled children and young people are at significant risk for sexual abuse not only because of their impairment and dependency on multiple caregivers but also social factors like inadequate sensitisation of members and safety precautions in residential settings. In addition, they are not heard or believed when they report, and their experiences are not afforded the same significance as those of other children.

Following sexual abuse, children with ID experience a range of psychopathology similar to that experienced by the general population. This includes traumatic stress reactions, depression, anxiety and behavioural problems like aggression, self-injury and sexual behaviour problems. Short-term impact of sexual abuse may include withdrawal from school, difficulties in communication and academic delay. Long-term effects of child abuse include fear, anxiety, depression, anger, hostility, inappropriate sexual behaviour, poor self-esteem, substance abuse and interpersonal difficulties (Sequeria & hollins, 2003).

## INTERVENTIONS FOR STRESS MANAGEMENT IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS

Cognitive, emotional and physical impairments in children with ID provide them with limited opportunities to overcome their stress (Hartley & Maclean, 2008). Therefore, it is essential to build skills within them so they can handle stressful events before they occur or when they occur. Overprotective parenting may be counterproductive leading to less exposure, under stimulation, and limited learning opportunities. A three-level of preventive, promotive and interventional approach is shown in the figure 3, which describes the need for caregivers to be pre-emptive in understanding the stressors, foster individual strength and attributes.

**Figure 3: Levels of prevention and intervention (overall the measures have to be used at various levels, interchangeably depending on the context of the individual patient and their needs)**



The treatment approaches can be individualized for a given child depending on his/her strengths.

Some basic principles to be followed in training a child with developmental disabilities in coping with stress are –

- 1] **Facilitate recognition of stress:** It is imperative that the child is taught to understand various emotions by labelling and naming them and behavioural cues related to emotions as subjective recognition of distress is essential in stress management. It is necessary for the parents to understand signs of stress and be proactive in understanding stressful situations in their day-to-day activities

- 2] **Adapt appropriate teaching techniques:** It is important to adapt training modalities according to an individual's strength such as – demonstration, modelling, role-play, storytelling, and use of visual media such as visual cues, videos, pictures and visual schedules. Observation of skills and breaking a specific task into small skill sets is also useful. It is necessary to teach them when they are not stressed, and the training should not overwhelm their cognitive and adaptive functions. It helps to use their caregiver as a trainer,

Some examples: Deep breathing can be explained using visual modalities and demonstration. Relaxation by – visual meditation using a picture they like, a long walk, aquatics (stretching in water) or listening to music can calm them easily. Adopting a relaxed posture can be taught by demonstration of the task in smaller steps like – feet on the floor, knees at 90 degrees, back straight, shoulder straight to side, head balanced and pointed up and so on.

## **FOSTERING RESILIENCE IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS**

Resilience is a dynamic process involving interactions between risk and protective factors both internal and external to an individual that mediate the influences of adverse life events (Alvord & Grados, 2005). It is important to understand various factors that act together both at an individual level within the person in interaction with their immediate environment including caregivers, school, employment, and society as a whole that make them overcome stressful situations with resilience.

**At an individual level:** Alvord and Grados identified that children with ID who were resilient in overcoming stressful situations demonstrate a strong desire to succeed, persistence, better understanding of their strengths and high level of motivation as defined by six major factors that include proactive orientation, self-understanding, self-regulation, connections, attachments, and school and community involvement. It is essential that the individual is supported by looking into their strengths, expectations, emotional and social support needs.

**At family level:** A secure attachment with caregiver, cohesive family atmosphere, positive adaptations by the parents in accommodating their life in terms of hope, maintaining their wellbeing, better understanding of child's needs, strengths and disability can enhance resilience by avoiding social exclusion, loneliness and discrimination (Alvord & Grados, 2005; Lunsky, 2008).

**At school level:** Educational and training services aimed at building inclusive education with supportive and safe environment tend to accommodate and remove barriers, increase their confidence and self-esteem by providing a safe environment that can develop friendship, peer group support, learning opportunities thereby reducing stigmatisation and discrimination. It is also essential that the support system should look into reported stigmatisation, bullying and discrimination in school (Hartley & Maclean, 2008).

## CONCLUSIONS

Stress correlates with severity of behavioural problems and impacts the quality of life of children with NDDs. It can even lead to caregiver burnout and adversely influence family functioning. Seemingly trivial stressors can cause significant distress and decompensate a person with developmental disability into greater extent than general population. It is, therefore, imperative to proactively educate caregivers about the likely stressors and ways of managing the same. It is equally important for clinicians to acquaint themselves with the atypical presentations, so the problem is identified early, and timely interventions are instituted.

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## **STRESS, CAREGIVERS AND MENTAL ILLNESS**

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### **OUTLINE**

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| 1. INTRODUCTION  | 2. QUANTITATIVE OVERVIEW OF CAREGIVER CONTRIBUTIONS          |
| 3. QUALITATIVE OVERVIEW OF CAREGIVER CONTRIBUTIONS         | 4. IMPACT OF CAREGIVING PROCESS ON THE CAREGIVER'S WELLBEING |
| 5. MENTAL ILLNESS AND CAREGIVER STRESS                     | 6. FACTORS INFLUENCING THE PERCEIVED CAREGIVER STRESS        |
| 7. NEED FOR THE ROUTINE ASSESSMENT OF CAREGIVER STRESS     | 8. ASSESSMENT AND EVALUATION OF CAREGIVER STRESS             |
| 9. CAREGIVER STRESS REDUCTION APPROACHES AND INTERVENTIONS | 10. CONCLUSIONS  |

## **INTRODUCTION**

A caregiver is described as, “one who provides care and assistance for any one who is, in some degree, incapacitated and requires some help” (Family caregiver alliance, 2005). The magnitude of the support as “unpaid or informal caregiving” provided by the family caregivers to people with disabling physical and mental disorders cannot be compensated by any formal healthcare service. It is estimated that more than 65 million people corresponding to about 29% of United States population care for chronically ill, disabled or aged family member or friend during any given year and spend an average of 20 hours per week in providing care for

their loved ones (National Alliance for Caregiving, 2009). Needs of persons with physical and sensory disabilities, supports required for them differ significantly in comparison to the needs of persons with mental illness related disabilities, and hence the supports required. In this chapter, we use the term caregiver to indicate family caregivers who provide, “varying degrees of support and assistance to their family members affected with mental disorders”.

Among several definitions for caregivers, perhaps one that describes better is, “individuals who provide care which is typically uncompensated and usually at home, which involves significant amounts of time and energy for months or years, and which requires the performance of tasks that may be physically, emotionally, socially, or financially demanding” (Biegel et al., 1991). Often, it would be more than one member of the family who would provide caregiving to the disabled dependnat family members, and a family member who contributes to more than half of the caregiving process is called as primary caregiver. Families serve as an extension of the formal mental health care delivery systems providing crucial case management functions such as monitoring the recovery, offering support during the crisis situations and offering advocacy inputs to relevant stakeholders involved in designing and delivery of mental health care programs (Saunders, 1997).

Few developed nations had recognized the importance of family caregivers and the magnitude of informal care they provide for their loved ones with mental disorders, and had devised specific policies and programs to support them. Carer or attendance allowance is paid for the elderly or disabled requiring continuous assistance in Germany, France and Austria. In United Kingdom (UK), Ireland and Australia too caregiving is treated similar to sickness or unemployment and therefore offers caregiver allowance, thou. Acknowledging the importance of contributions made by caregivers, and the need for recognition of the caregivers under the law too, section 2 of the Mental Health Care Act (MHCA) 2017 defines caregiver as, *“a person who resides with a person with mental illness and is responsible for providing care to that person and includes a relative or any other person who performs this function, either free or with remuneration”* (Mental Health Care Act 2017). Section 24 of the Rights of Persons with Disabilities Act 2016 mandates that appropriate governments should provide caregiver allowance for family caregivers supporting those who are certified as persons with high support needs ( Rights of Persons with Disabilities Act, 2016).

## QUANTITATIVE OVERVIEW OF CAREGIVER CONTRIBUTIONS

According to the Centre for Disease Control and Prevention (CDC) in the year 2009, about 25% of adults in United States of America (USA) had provided informal or unpaid care to persons with some form of long-term illness with in. One-year value of this unpaid caregiver activity is estimated as about US \$ 450 million. (CDC, 2009). Family caregivers are reported to be more likely to be women (61%) than men(39%) suggesting a gender factor. Influence of gender factor appears to be consistent across cultures, as it is observed that women are more likely to be caregivers for elderly in southern India than men (Narayan et al, 2015). A large number of caregivers are middle aged with median age of around 50 years for a typical caregiver (Caregiving in the USA, 2020). European Union wide data based on Eurofamcare study suggests that about 76% of main carers for older people are women. In this study it is observed that a half of the carers are children of the elderly people requiring care, and 22% were either partners or spouses. (Glendinning et al, 2009). There are no large scale and methodical studies in India about the caregiver numbers and their contributions. However, National Mental Health Survey (NMHS) of India estimation of point prevalence, as 1% for severe mental illnesses (SMI) like schizophrenia, bipolar affective disorder (BPAD) and as 10.6% for any mental disorder in people aged above 18 years excluding nicotine use disorders is often used for public mental health policy and funding (Gururaj et al., 2016). Indians being more family centric in their societal lifestyle in contrast to western societal individuals, it may be inferred that about 1-10% of Indians are involved in the caregiving process of their family members affected with one or other mental illness.

## QUALITATIVE OVERVIEW OF CAREGIVER CONTRIBUTIONS

Family caregivers take up countless responsibilities in assisting their dependant family members, which often depend upon the nature of illness, phase of illness and impairments in functionality due to illness apart from many other psycho socio cultural factors. A survey conducted in USA revealed that shopping for groceries, transportation to doctor appointment, cooking, meal preparation, housekeeping such as laundry, reminders to take medication, administering medication, managing finances, bathing, toileting are the areas in which caregivers assist the dependent family members as part of informal caregiving (Statista, 2020). Assistance required for people with chronic and severe mental illness like Schizophrenia and

BPAD may involve more support in ensuring compliance to treatment, financial, work domains and less assistance in bathing, toileting compared to people with progressive conditions like dementia, where caregivers may have to assist in activities of daily living like feeding, bathing, toileting and ensuring safety, administering medication, etc.

## **IMPACT OF CAREGIVING PROCESS ON THE CAREGIVER'S WELLBEING**

Caregiving process can be demanding, exhaustive imposing stress along with a sense of satisfaction depending on a range of factors which would be discussed more in the following sections of this chapter. Caregiver appraisal is the term proposed for assessing the impact of caregiving on caregivers, which consists of two components, caregiver satisfaction and caregiver burden highlighting that experience of caregiving is a mixture of emotions rather simply a burden or stress (Lawton et al, 1991). It is not uncommon for family caregivers to describe a range of positive aspects of caregiving like a sense of role satisfaction and reciprocity by doing their best, a sense of personal growth by increase in self-awareness, a sense of mastery and competency by acquiring transferrable problems solving skills, and a sense of faith and spiritual gains (Lloyd et al, 2016) Predictors of caregiver satisfaction in the caregivers of people with dementia are, having a consanguineous relationship with the care recipient, perceived lower burden and manageability in spite of higher cognitive impairments (de Labra et al, 2015). It is clear that caregiving is not always perceived as a burden on those who provide time and effort towards caring for their family members affected with SMI. However, caregiving process can induce stress, exhaust the caregivers and place undue burden especially if they have other roles and responsibilities to fulfil.

## **MENTAL ILLNESS AND CAREGIVER STRESS**

Although caregiving is a part of every family system, it becomes challenging when caregiving has to be extended to a family member with mental illness, with functional limitations and disability for prolonged periods. Caregivers of persons suffering from chronic and severe mental illnesses often describe challenges in their personal life, career prospects, reduced social life, maintaining leisure activities, financial independence, time spent at work, performance at work, potential for earning, quality of life, physical health issues, etc (Awad & Voruganti, 2008; Bademli & Lok, 2020). Caregiver burden is described as “a perception of

psychological distress, anxiety, depression, demoralisation and loss of freedom attributed directly to caregiving". Caregiver stress and caregiver burden are often used interchangeably and in this chapter we use caregiver stress term to indicate both. A range of experiences like anxiety, depression, anger, sleeplessness, irritability, lack of concentration, social withdrawal are loosely described as caregiver stress, when they have a temporal correlation with the responsibility of caregiving. Impact of caregiving can be across the domains of life which includes few or all of the above mentioned experiences suggesting psychological impact. Alzheimer's association of USA reports that about 17% caregivers of people diagnosed with dementia had quit their jobs before or after assuming the role of caregiver, and about more than 50% of employees arrive late to the work or leave early from work when they have caregiver responsibility to someone they love (Alzheimer's association, 2015). A taxonomy of economic costs experienced by the caregivers identified three broad domains under which such costs may be estimated for a public health policy, which are employment, out of pocket expenditure and costs of caregiving labour in addition to several sub domains (Keating et al., 2014) It is estimated that for caregivers aged above 50 years in USA this economic loss under various heads could be around US \$ 3 trillion (Family Caregiver Alliance, 2016).

## **FACTORS INFLUENCING THE PERCEIVED CAREGIVER STRESS**

Various observations that a few caregivers cope well than others indicate that there are many factors which influence the experience of stress in caregivers. A list of such factors observed to contribute or exacerbate the perceived caregiver stress is described below under various sub headings (Raina P et al., 2005; Chadda RK. 2014; Azman A et al., 2017; Jafari H et al., 2018; Rahmani F et al., 2018; Serra L et al., 2018).

### **A. Factors related to impairing illness and care recipients**

- 1) Nature and severity of the mental illness
- 2) Recipient's (patient's) disruptive behaviours
- 3) Inadequate recovery and the need for prolonged care
- 4) Degree of disability and dysfunctionality
- 5) Amount of time spent in caregiving

**B. Factors related to caregiver**

- 1) Having only a few years of formal education
- 2) Unpreparedness for caregiving role
- 3) Low self-esteem.
- 4) Dysfunctional coping strategies
- 5) Need to fulfil more than one role
- 6) Physical and mental wellbeing of the caregiver
- 7) Lack of choice in being a caregiver

**C. Psychosocial factors**

- 1) Social discrimination and stigma
- 2) Lack of supportive resources from others
- 3) Disruption of family functioning
- 4) Low gross income of the family
- 5) Inadequate mental health support systems

As described above a range of factors, and hence the demands it places on the caregivers has impact on caregiver stress. Following are a few examples of such variance in perceived caregiver stress with regards to psychiatric disorder diagnosis. Severity of symptoms both positive and negative symptoms of schizophrenia are reported to be associated with higher perceived levels of caregiver burden (Awad & Voruganti, 2008). Age of the caregiver, duration of the illness, gender of the patients are observed to have impact on perceived caregiver burden in people caring for patients with schizophrenia (Kumar et al., 2015). Findings from Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) suggest that patient problem behaviours, role dysfunction, and disruption of household routine as important contributors to the level of perceived caregiver burden. In a comparative study in this regard between caregivers of patients with schizophrenia to patients with BPAD, caregivers of people with Schizophrenia apprised their experiences more negatively in comparison with the caregivers of people with BPAD (Grover et al, 2012). People caring for patients with obsessive compulsive disorder (OCD) too reported a poor quality of life, higher family burden, disturbed social relationships, depression (Gururaj et al., 2008; Grover &

Dutt, 2011). Among the family caregivers providing care for people with substance use related mental disorders a higher care giver burden is reported among wives of the husbands with alcohol dependence (Shekhawat et al., 2017).

## **NEED FOR THE ROUTINE ASSESSMENT OF CAREGIVER STRESS**

The caregiver burden is a constant source of stress and the way the caregiver copes, affects the course of illness of the patient . Poor quality of life experienced by the caregivers can impact the quality of caregiving and therefore may impact the mental health outcomes and interpersonal relationships between care recipients and caregivers. Family Caregiver Alliance of USA estimated that caregivers provide about 37 billions of unpaid or informal care to their adult family members or friends annually. In a similar estimation from Germany as cited in a university report on informal caregiving impacts (Baur & Sousa-paza, 2015) it is estimated that about 4 million Germans are care providers providing informal care corresponding to 4.9 billion hours (Schneider, 2006). If such is the estimated magnitude of the caregiver's contribution in the USA and Germany, it would be perhaps hundreds of billions of hours of caregivers time in non-western countries in this regard where family cohesiveness is more than western countries. It becomes necessary to care the caregivers who contribute to this billions of hours of informal caregiving, as any deficits in this system could raise the demand for the same care from professionals. Considering the importance of caregiver's role in the process of mental health care, and in the process of rehabilitation of people with SMI, a routine assessment and formal evaluation wherever required for caregiver appraisal by the mental health professionals is necessary to ensure optimal outcomes. State's human and economic resources won't be sufficient to provide the care offered by family care givers in continuous and informal way, and the best thing that health care systems can do is to support the informal caregiving by supporting the family caregivers. US family caregiver Alliance recommends that it is important to recognise, respect and to assess the caregiver needs as they form core part of long term services and supports for people requiring continues caregiving. Such assessment should be family centric considering the care recipient and care provider perspectives, and assessment should result in development of a plan indicating the provision of services and measurable outcomes. Caregiver assessment should use culturally competent practices by experienced people in that field and assessment should be multidimensional with a periodic assessment (Feinberg, 2020). Investments made

for understanding the factors contributing to family caregiver stress and designing programs, systems, supportive networks for assisting the family caregivers can have a positive outcome on the individuals with mental disorders, their families and thus on the entire society. Early identification of caregiver stress and features suggestive of caregiver burnout can help the mental health professionals to consider appropriate strategies to evaluate further and to intervene as per the requirements. (Walke et al., 2018). Bauer (2015) argues that as caregiving arrangements can be heterogeneous a flexible public support is needed to adapt to the caregiver needs and he suggests that a system to support a proportionate compensation to the negative outcome on employment and health of the caregiver should be created. Caring of the caregivers is gaining as a public health policy recommendation. European countries appear to have understood the importance of “investing in caring for the caregivers”, which may be inferred from their funding support to various programs intended to support caregivers. A few of them are Preventive support programs for carers of mental health patients in Netherlands, Siblings Programme in Italy, Action Programme in UK, Time off for family carers in Austria, Carer’s Leisure Pass of England, Right to paid work leave in Netherlands, Right to request flexible work timings in England. (Glendinning et al., 2009).

## **ASSESSMENT AND EVALUATION OF CAREGIVER STRESS**

During routine follow-up and evaluation of patients with SMI, mental health professionals (MHP) should always consider a multidimensional and comprehensive needs assessment as far as possible. However, in resource limited settings such detailed and routine assessments may not be feasible. A simple enquiry about the psychological and physical well-being of the caregiver, functional ability or limitations, challenges, if any, faced by the caregiver, supports available, financial hurdles associated with caring for patient, ability to find time to self and to socialize with friends or family could be a way to begin. MHP should be sensitive to identify any verbal or non-verbal cues indicating the distress in caregivers, and should proceed with enquiries about the variations, if any, in the mood, feelings, energy levels, self-esteem, sleep, hopefulness etc. Any one or more of the following lists should raise the suspicion about possible negative impact of caregiving on the well-being of caregivers.

- a. feeling overwhelmed or constantly worried
- b. feeling of tired often

- c. getting excess sleep or not enough sleep
- d. gaining or losing weight
- e. irritability
- f. reduced interest in activities
- g. feeling sad or depressed
- h. frequent headaches, bodily pains or other physical problems
- i. changes in the patterns of usage of substances including prescribed medications.

Any positive indication that caregiver is experiencing undue stress that requires a formal evaluation should be assessed on a priority basis by detailed clinical assessment including tools such as the following which either can be rated by the caregiver or can be rated by professionals (APA, 2011). In addition to informal assessment and a formal clinical evaluation a range of tools may be used to understand the perceived caregiver stress and psychological wellbeing in carers for appropriate planning to address caregiver stress. A few are listed below.

**A few tools to assess caregivers caring for adults**

- 1. Zarit Burden Interview
- 2. Perceived Benefits of Caregiving
- 3. Picot Caregiver Rewards Scale
- 4. Caregiver Reaction Scale

**A few tools to assess parent -caregivers**

- 1) Impact on family scale
- 2) Parenting stress index

**A few tools used to assess caregiver coping**

- 1. Perceived Support Scale
- 2. Coping Health Inventory for Parents

**A few tools used in Indian population**

- 1. Burden Assessment Schedule
- 2. Caregiver Burden Scale – Indian Population

## CAREGIVER STRESS REDUCTION APPROACHES AND INTERVENTIONS

As perception of caregiver stress can be unique to individuals based on a range of factors, a better understanding of exacerbating and protective factors in this regard is essential for mental health professionals. A few characteristics and factors which are observed to predict lesser caregiver stress experience in comparison to those who express higher degree of caregiver stress are, good perceived social support, engaging in social support groups, use of stress management strategies, learning the positive coping strategies used by other caregivers, having a sense of mastery over caregiving situation, resilience, high self-esteem (Raina et al., 2005; Azman et al., 2017; Serra et al., 2018).

Identification of factors contributing to caregiver stress and periodic assessment of psychological wellbeing of the caregiver by trained mental health professionals is crucial in the process of caring the caregivers and to ensure optimal functioning of this extended healthcare system. Addressing the factors contributing to caregiver stress experience like financial hurdles, respite care, crisis management etc., can play a significant role in the reduction of perceived caregiver stress experience. In addition to these, mental health professionals should facilitate the caregivers access to accurate information about the illness, information about available support systems under governmental and non-governmental organizations, interaction with similar family caregiver groups, all of which may improve the resilience of caregivers. A range of non-pharmacological interventions designed to increase the patient engagement in some form of meaningful engagement away from the family like engagement in day-care service centre are reported to improve the psychological wellbeing of the family caregivers. Day-care services for keeping people with SMI to be engaged during day time offers respite care to the caregivers, in addition to improving the community participation and socialization of people with chronic and severe mental illnesses. Day care services for people with severe and chronic mental illnesses is a well-established concept in developed countries like USA and it is gaining momentum in developing countries too. MHC Act 2017, which mandates the establishment of such range of community based services intended to improve the community participation of people with SMI can be a game changer, if implemented in its word and spirit, in improving the quality of life and well-being of the family caregivers. Though there are a few such day-care centres across major cities in India under governmental and private sectors,

the State of Karnataka is the first state to start such day-care centres one per each district in India, in public private partnership under the name “Manasadhabra”. Possibly other states soon follow the footsteps of Karnataka state in creating community support systems which could reduce the caregiver burden in indirect manner. Family caregivers of people with SMI have formed associations to help themselves, to help other family caregivers, to negotiate with policy makers in creating user friendly programmes and to advocate on policy making. Among many such caregiver associations, National Alliance on Mental Illness(NAMI), Family Caregiver Alliance (FCA) from USA, Association of carers and Family Carers Network from UK, Schizophrenia Awareness Association, Families Alliance on Mental Illness, Parivaar, Action for Autism, and Spastics Society of Karnataka from India are just a few. A knowledge of these organizations to mental health professionals is essential as facilitation of a caregiver contact with such nearby supportive networks can be a small but great step in addressing the caregiver stress in family members caring for people with SMI.

## CONCLUSIONS

Across the nations, informal caregivers are now regarded as valuable resource adjunct to formal mental health care delivery systems, and policies are being designed to support them by providing financial and other necessary social supports. Mental health professionals should be aware of the construct of caregiver appraisal, and such appraisal should be a part of routine follow up consultation for all the people having a chronic mental illness, and who are supported by their family members. A failure to care the caregivers, and inadequacies in addressing the stress in caregivers, which may accumulate due to the caregiving process could impose undue burden on formal mental health care delivery systems.

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## **STRESS AND CRIME**

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### **OUTLINE**

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| 5. DO ALL PEOPLE WITH STRESS COMMIT CRIME? | 6. CRIME AND STRESS                     |
| 7. TREATMENT IMPLICATIONS                  | 8. CONCLUSIONS                          |

## **INTRODUCTION**

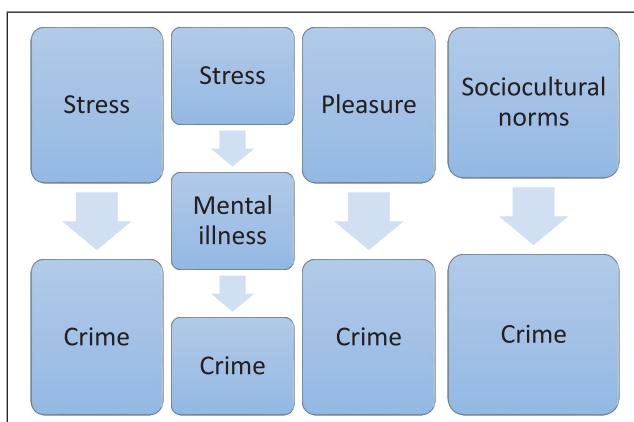
The term ‘stress’ was coined by Hans Seyle, who defined it as “a non-specific response of the body to any demand” (Tan & Yip, 2018). It can also be defined as the degree to which you feel overwhelmed or unable to cope as a result of pressures that are unmanageable (Mental Health foundation, 2015). It is subjective. The perception of stress depends upon multiple factors which can be environmental, social, economic, genetic factors, etc. (Mental Health foundation, 2015). The physiological responses to stress can be either by flight, fight, or freeze technique. It is during the fight response that violence can be seen. Stress doesn’t just act immediately to increase aggression, but also in long term, stress leads to changes in multiple neurochemical pathways leading to emotional dysregulation and impaired threat perception which ultimately leads to increased aggression, violence, and crime.

Crime is a behaviour that violates the criminal law. The causes of crime are complex such as poverty, parental neglect, low self-esteem, sensation/pleasure seeking, mental illness, alcohol and drug abuse can be connected to why people break the law (Lynch et al., 2015). Many of these causes revolve around the poor coping with the demands of the society. Some are at greater risk of becoming offenders because of the circumstances into which they are in..

Crime can be conceptualised to occur because of different reasons as below (Fig 1).

1. Crime can also occur because of stress, which leads to maladaptive behaviours and then lead to crime. There is no mental illness in this pathway.
2. Crime can also because of development of mental illness developing secondary to stress. Stress can lead to different mental illnesses like psychosis, depression, post-traumatic stress disorder (PTSD), anxiety disorders, substance use disorders, dissociation, etc., These disorders can lead to impaired judgment and criminal acts.
3. Crime can occur in the context of “need for pleasure” for e.g rape, robberies, etc
4. Few acts are considered as crime because of prevailing socio cultural norms. For example, homosexuality, child pornography and blasphemy laws are viewed differently in different cultures. Homosexuality was considered as crime in India till it was decriminalised recently. Whereas, other western countries, it was legally accepted. Even blasphemy laws are different in different countries depending upon their socio-cultural norm.

**Figure 1: Different Pathways of Crime.**



Our chapter exclusively focuses on the first two pathways where stress plays a central role in causation of crime. We are not discussing about the crimes where need of pleasure is the main driving force behind the commitment of crime. Further as per Cesare Lombroso's theory of 'born criminals', criminality arises out of biological composition (genetics) of oneself, again here also stress does not play a significant role, so we are not including this as well in our discussion (Ferracuti, 1996).

## **THEORIES EXPLAINING STRESS AND CRIME**

Multiple theories have been proposed to explain the occurrence of crime and few among them have focused on stress as a central factor in the causation of crime, such as Merton's strain theory and Revised general strain theory by Agnew. In this chapter, the above-mentioned theories.

### **a. Merton's strain theory (Merton, 1938)**

Merton postulated that when an individual is unable to meet his financial goals through legitimate measures, he/she will choose illegal or illegitimate pathways to attain his/her goals. However, this theory faced a lot of criticism as it could not explain crimes arising out of stress because of reasons other than financial stress. This theory also focused on the crimes committed by people of lower socio economic class and could not explain the crimes done by those belonging to higher socioeconomic class. Also, not all individuals cope with illegitimate measures and only why specific individuals choose illegitimate measures was not explained in this theory(Agnew, 1992, 1985). These shortcomings were addressed by the following Agnew's revised general strain theory.

### **b. Agnew's revised general strain theory (Agnew, 1992, 1985)**

Agnew did not agree with the opinion of Merton about the causation of crime. He believed that the strain is not just caused by financial factors, but it can also be caused when one's aspirations towards any goal are not met. He also proposed two additional sources of strain namely removal of positive stimuli and confrontation of negative stimuli. For instance, loss of one's job is removal of positive stimuli, and bullying a child is a confrontation of negative stimuli. So as to include all those other factors which can cause strain this particular theory was proposed. Different forms of strains that the individual could face are parental rejection, inconsistent parenting poor educational performance, child abuse, abusive peer relations etc.

the above strains will lead to negative emotional states like anger, fear, & sadness. When persons deal with these negative emotions by using poor coping mechanisms crimes are likely to occur. So, the individual's coping strategy becomes the determining factor in leading to crime, and this received importance in this theory. This theory was successful in explaining domestic abuse, sexual assault, gambling, drug and substance use along with financial stress leading to crime (Agnew, 1992).

## **FACTORS CONTRIBUTING TO CRIME**

Factors contributing to increased aggression/violence/crime can be conceptualized as occurring over a continuum from the prenatal period to the period immediately before the occurrence of crime. So, these factors are best understood when seen from the life cycle perspective. In the subsequent paragraphs, we discuss the various factors and how they act through increasing stress and lead to aggression/violence and crime.

### **1. Pre-birth factors**

Pre-birth factors include genetic influences, prenatal conditions, and perinatal factors and the interaction between all these factors. Prenatal factors are the intrauterine environmental factors and perinatal factors include obstetric complications and health problems around the time of birth. Intrauterine environmental factors include maternal smoking, drinking, substance use, infectious diseases, and exposure to toxic environments (Almond, 2006) and these are directly related to the mental and physical health of a child (including birth weight), and cognitive abilities. They are known to be associated with antisocial behavior, including crime (Mednick & Kandel, 1988).

### **2. Post birth factors**

Many researchers believe that the etiology of crime is related to post-natal factors like social mechanisms (e.g., poverty), behavioral mechanisms (e.g., role modeling), psychological mechanisms (e.g., childhood traumas and abuse), and biological mechanisms occurring just after birth (e.g., a head injury or exposure to environmental toxins, such as lead). The mechanisms that are most relevant in this context are those that can help explain criminal behavior and, at the same time, generate parent-offspring correlations (Hjalmarsson & Lindquist, 2013). Stress provokes the classical response of 'fight' 'flight' or 'freeze', among which "fight" response leads to violence, aggression and crime

### **3. Factors in childhood**

#### **3.1 Adverse Childhood Events (ACEs)**

There have been consistent reports of the association of ACE and crime (Levenson & Socia, 2015; Perez et al., 2018; Scottish, 2018). ACEs are stressful experiences that occur in childhood, which can be either direct harm to the child (e.g. maltreatment) or affecting them through the environment in which they live (e.g. growing up in a house with domestic violence) (Bellis et al., 2015). ACEs can be physical, verbal, sexual abuse, physical and emotional neglect, domestic violence, parental separation, substance abuse, incarcerated relative, and mental illness (including substance use) in family members (Felitti et al., 1998). The children exposed to ACE will develop disturbances in the attachment patterns and are more likely to get involved with risk-taking behaviors as adults, leading to physical health, mental health, and legal consequences. Children living in environments with violence, assault, and abuse are more likely to develop such traits themselves as these behaviors are normalized, leaving them more likely to both committing violence/or be the victims of violence in adulthood (Bellis et al., 2015). Furthermore, ACE can make the individuals feel unworthy and a develop propensity for engaging in such behaviors in quest of short-term relief. This makes individuals develop poor coping behaviors such as smoking, alcohol consumption, poor diets and even early sexual activity (Bellis et al., 2015). Lack of education or dropout from school makes the children more likely to display antisocial behavior (Sharma et al., 2016). It has been shown that poverty, broken family, and history of criminality in the family act as predictor variables for substance use and criminality among children (Sharma et al., 2016). Recent evidence shows that chronic traumatic stress in early life alters the development of a child's brain and can alter the development of the nervous, hormonal and immunological system (Broyles et al., 2012; Danese & McEwen, 2012). There is strong association between ACEs and vulnerability to harm others, which means the children of those who experienced ACEs are at increased risk of being victims of ACEs (Renner & Slack, 2006). This is called the 'cycle of violence'(Sethi et al., 2018). A child who has been a victim of sexual abuse has a high chance of getting engaged in criminal activities including sexual offenses. Gold et al., 2011, studied the relationship between abusive parenting and violent delinquent behavior. The findings of the study concluded that the subjects who converted shame (i.e., low expressed shame, high blaming others) had more exposure to abusive parenting and showed more violent delinquent behavior than their peers who showed expressed shame (i.e., high expressed shame, low blaming others) (Gold et al., 2011). Kozak et al., 2018

showed that female victims of Child Sexual Abuse are 1.7 times more likely to engage in violent and delinquent behavior (Kozak et al., 2018). The Welsh ACE study, 2015 reported that people with ACE are 14 times more likely to be a victim of violence, 15 times more likely to be a perpetrator of violence in the last 12 months, and 20 times more likely to have been incarcerated in their lives (Bellis et al., 2015). Perez et al., (2018), showed that higher ACE scores predict maladaptive personality traits like aggression and impulsivity which in turn predicts adolescent problems like substance use, deviant peer imitation, mental illness and leading on to serious, violent, and criminal delinquency (Perez et al., 2018).

Chronic stress because of ACE can lead to functional and volumetric changes in anterior cingulate cortex, hippocampus, and amygdala (the brain areas involved in emotional regulation, memory and stress management). The above changes will lead to impairment in decision making, self-regulation, memory, fear processing and stress management leading to development of borderline personality as adults.

### **3.2 Psychiatric illness in childhood**

Psychiatric illness in childhood includes attention-deficit disorder, disruptive behavior disorders, and mental retardation (Guze, 1995). Mental retardation is a disorder with arrested brain development, this has been linked to increased aggressive responses and incapacity to realise the legal implications of their behaviour, there is no role of stress directly in this subgroup, but patients of mental retardation lack ability to deal with stress due to their cognitive deficiency (Accardo & Capute, 1998; Prins, 2015). Aggressive behavior, property destruction, breaking rules are symptoms of conduct disorder, which is a disruptive behavior disorder, is linked to the crime. Oppositional defiant disorder (ODD), which is characterized by persistent hostile or disobedient behavior aimed at authority figures is another crime-linked disruptive behavior disorder (Guze, 1995). ODD and CD are linked to juvenile delinquency and ASPD in adulthood. The development of CD and ODD and partially explained by ACEs, thereby emphasising the role of stress in development of these disorders and violence / crime in adulthood(Foley et al., 2004).

### **4. Socio-economic factors**

Various socio-economic factors like being unemployed, being poor, being from disadvantaged social class leads to financial and social stress. As already explained by the two most popular theories of crime, that is Merton's strain theory and

Agnew's revised general strain theory, the above factors are risk factors for crime. According to the United Nations Office on Drug and Crime (UNODC) report, during periods of economic stress like a natural disaster, economic slow down, the incidence of robbery, homicide and motor vehicle theft also increase (United Nations, 2012). Hindelang, 1979, found that the people from lower socio-economic class exhibited a greater tendency in terms of violent crime and the rates of minor crime were consistent among all social classes. This was further supported by the fact that rates of drug use, are consistent among all social classes (Hindelang et al., 1979).

## **5. Factors in adulthood**

### **5.1 Psychiatric illness**

Adults are also exposed to stress like social, economic, and other traumatic events. Men are more likely to experience combat trauma, physical attacks, being threatened or kidnapped and women report experiences related to exposure to rape, and sexual molestation, neglect, and childhood abuse (Friel et al., 2008). Stress can lead to psychiatric illnesses like depression, substance misuse, acute stress reactions, post-traumatic stress disorder (PTSD), and personality change. Psychiatric illness can lead to violence and crime by themselves. Many studies are indicating an association between the major mental disorder and violence especially more with schizophrenia (Joyal et al., 2007). The following evidence focus on psychiatric illness and crime.

#### **5.1.1 Severe mental disorders & Crime:**

Schizophrenia is associated with 4 to 6-fold increased risk of violent behavior and these are preventable causes of crime (Fazel et al., 2009). The conceptual model of violence in schizophrenia postulates that patients are violent as a result of the symptoms in the disorder itself (eg, delusions, hallucinations) (Swanson et al., 2006). It may also be secondary to comorbid substance use, which is an established risk factor for violence (Grann & Fazel, 2004). An alternative model is that schizophrenia and violent behavior co-occur because of presence of other risk factors like past violence, physical abuse, juvenile detention, parental arrest record, recent divorce, unemployment, victimisation etc (Fazel et al., 2009; Varshney et al., 2016). However, the link between schizophrenia and crime is not well established and well treated patients of schizophrenia pose no more risk of crime than the general population(Volavka & Citrome, 2011).

### **5.1.3 Substance use disorders & Crime:**

Substance use is an independent risk factor for violence (Grann & Fazel, 2004). Studies have examined the role of alcohol in violent offending, violent victimization, and intimate partner violence (IPV) and even after adjusting for the confounders, alcohol abuse/dependence increased the risk of violent outcomes by 2–3-fold. The same study also found that alcohol use disorder accounted for 5–9% of the violent offending/victimization and IPV perpetration in the cohort.(Boden et al., 2012). In another longitudinal study, where adolescents were followed-up from 13 to 27 years of age, it was found that cannabis was linked to drug-related offenses (Pedersen & Skardhamar, 2010) and alcohol to violent behavior (Norström & Pape, 2010). The National Longitudinal Study of Adolescent Health is a cohort study in the United States found strong relationships between alcohol consumption and criminal behavior & victimization for both men and women (Popovici et al., 2012). Sharma et al., 2016 demonstrated that substance use has direct effects on criminal behavior and violence. Individuals with substance use exhibit violent behavior to obtain drugs, e.g. theft, prostitution, procuring, and selling of narcotics. This can be explained with conception by Goldstein, which established relationships between substance use and violence. It needs to be distinguished between (a) psychopharmacological effects of the substance on behavior, (b) economic effects, violence to obtain money to procure substances and (c) systemic effects, which emerge as a result of sale and distribution of drugs (Goldstein,1985). The drug–violence relationship is further complicated by intoxication, and withdrawal effects of substances like heroin, alcohol, or inhalants (Sharma et al., 2016).

### **5.1.4 PTSD & Crime**

PTSD occurs as a consequence of a trauma. However, PTSD itself can lead to crime. It may be due to a direct association between the features of PTSD like anger or the core features of PTSD including flashbacks, sleep disturbance, labile mood, and increased anxiety. PTSD is also associated with depression and substance misuse (Kessler et al., 1995; Solomon & Davidson, 1997) and these comorbidities have an established relationship with aggression via disinhibition or an increase in impulsivity (Friel et al., 2008).

### **5.1.5 Dissociation & crime**

Dissociation may mediate the ‘cycle of violence’ and sometimes (almost a third of homicides), there has been amnesia of the crime committed. Increased dissociation is associated with increased violence in many including college students, young

mothers, military veterans, psychiatric inpatients and outpatients, and sexual, domestic violence, and homicide offenders. Pathological levels of dissociative experiences have been reported in about one-quarter of the inmates (Moskowitz, 2004). The phenomenon of dissociation in forensic psychiatry is poorly understood due to the lack of clear definitions. Dissociation takes different forms, it may be a disorder by itself or maybe a symptom of another disorder. Its relevance in forensic psychiatry is unclear. There are various instances where it has gained importance when defendants' claims of having had a dissociative experience at the time of criminal action (Bourget, 2017). The case of Bianchi, a serial murderer had convinced a few experts that he had multiple personality disorder and later admitted that he had faked the disorder (Bourget, 2017; Watkins, 1984). So, the concept of malingering also must be kept in mind while evaluating such people. The above-mentioned evidences summarize the link between various psychiatric illnesses and crime.

## **NEUROBIOLOGY OF STRESS AND CRIME**

ACEs can have significant effects on the normal development of various neuroendocrine and neurobiological systems. ACEs can lead to structural and functional brain alterations such as changes in BDNF expression, increases activity of amygdala and reduces the volume of limbic system (Bellis et al., 1999; Heim & Nemeroff, 2002; Kim et al., 2018). These alterations can further lead to emotional dysregulation, poor coping and conduct-related problems in childhood thereby leading to criminal behaviors in adults (Levenson & Socia, 2015). The following few paragraphs discuss various neurobiological mechanisms involved in the pathway of stress and aggression.

### **1. Hypothalamic-Pituitary-Adrenocortical (HPA) axis**

The HPA axis is one of the principle pathways to respond to a stressor. HPA axis activation consists of the release of corticotropin-releasing hormone (CRH) and vasopressin from the paraventricular nucleus of the hypothalamus (PVN) into the anterior pituitary gland. They stimulate the secretion of adrenocorticotropic hormone (ACTH) into the blood. ACTH stimulates the adrenal glands to produce and release glucocorticoids i.e cortisol in humans. The activity of the HPA axis shows diurnal variations, important for the regulation of physiological and behavioral processes during day-night cycles and during stress exposure (Young et al., 2004). The HPA axis plays a key role in aggression regulation(Kim & Haller, 2007). High HPA axis responses are often related to a state of hyperarousal. It

has been associated with high aggression in many psychiatric disorders, especially mood disorders (McBurnett et al., 2005; van Bokhoven et al., 2005). Chronically low HPA axis activity has been often linked to a hypo arousal state and this has been associated with high aggression in conduct and personality disorders (McBurnett et al., 2000; Susman, 2006; van Goozen & Fairchild, 2006). Studies have shown that reduced plasma glucocorticoids leads to changes in the prefrontal cortex, medial and central amygdala, and serotonin and substance P neurotransmission there by leading to development of antisocial personality disorder, conduct disorder and PTSD (Virkkunen, 1985; Yehuda, 2001; Kim & Haller, 2007). Thus, a hyper- and a hypo-active HPA axis is associated with increased aggression in various conditions

## **2. Vasopressin**

Vasopressin is a neuropeptide synthesized in the hypothalamic paraventricular nucleus, supraoptic nucleus, suprachiasmatic nucleus, extrahypothalamic nuclei, the bed nucleus of the stria terminalis, and the medial amygdala. Vasopressin stimulates the release of ACTH from the anterior pituitary in the presence of CRH and regulates body fluid and electrolyte homeostasis. Vasopressin also plays a key role in the regulation of emotional (anxiety, stress coping) and social (social attachment, parental care, social recognition, aggression) behaviors (Engelmann et al., 1996; Landgraf & Neumann, 2004; Caldwell et al., 2008; Veenema & Neumann, 2008). During the early postnatal period the mother-infant relationship consists of important behaviors like social attachment and bonding, which are strongly regulated by vasopressin and oxytocin (Feldman et al., 2007; Lévy et al., 1995; Veenema & Neumann, 2008). Disruption of the early social interactions alters the development and expression of social behaviors and this may be mediated via the vasopressin system. There are also indications that vasopressin plays a role in the regulation of aggression. In a study by Coccaro et al., 1998, a positive correlation was found between a life history of aggression and CSF levels of vasopressin in patients with personality disorders (Coccaro et al., 1998). Besides, intranasal vasopressin administration increased perception of danger and threat to neutral human facial expressions and decreased perception of friendly faces (Thompson et al., 2004, 2006).

## **3. Serotonin**

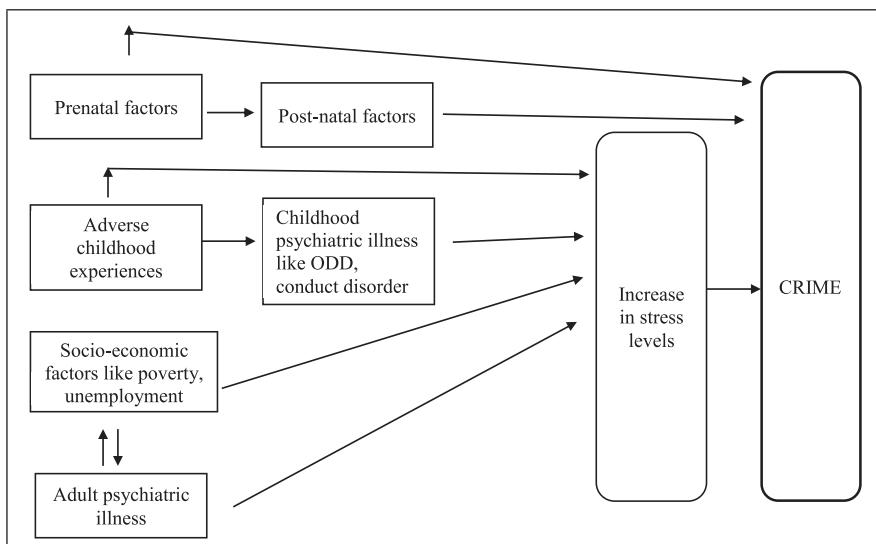
5-hydroxytryptamine (5-HT) is produced in brain stem raphe nuclei. During the postnatal period, 5-HT modulates the development of the central nervous system acting as a neurotrophic factor (Gaspar et al., 2003). Several studies demonstrated

that violent and aggressive are associated with the low 5-HT function (Linnoila & Virkkunen, 1992; Miczek et al., 2002; Takahashi et al., 2012; Westergaard et al., 1999), demonstrating that 5-HT inhibits aggression. However, 5-HT1A or 1B receptor agonists decrease aggressive behavior and was associated with a decrease in brain 5-HT release (Cunningham & McGinnis, 2008; Olivier, 2004). Aggressive behavior is associated with an increase in 5-HT neuronal activity (Hartline et al., 2017; van der Vegt et al., 2003). These paradoxical findings can be merged by proposing that an acute increase in 5-HT activity is required for normal and adaptive levels of aggression (e.g. display of adult dominance behavior) while a long-standing reduced 5-HT activity might be associated with inappropriate adult aggression (Veenema, 2009).

## DO ALL PEOPLE WITH STRESS COMMIT CRIME?

The relation between stress and crime is complex. Multiple factors act through multiple pathways there by leading to increase in stress and commitment of crime. We have made attempt to picturize those pathways in figure 2, which can be called as “Web of Stress and Crime”. Mere presence of stress is not sufficient for commitment of crime, but the way the stress is perceived plays a significant role. This is called “appraisal of stress”: Appraisal is how one perceives the circumstances in life. It differs from different people.

FIGURE 2: Web of Stress and Crime



For example, while one individual might experience anger, another may respond with features of depression. These factors have led the researchers to go beyond the stressors, to study the individual differences in the appraisal of stress (Green & Kane, 2009). Lazarus and Folkman, gave the reciprocal relationship between emotion and coping (Folkman, 2013). For every stressful experience, the individual has a cognitive appraisal that leads to an emotion and then a coping mechanism that leads to the emotional outcome. This theoretical perspective gives the reason behind the individual variability of stressful experiences.

## **CRIME AND STRESS**

Crime can lead to stress in the victims and they are more prone to experience anger, depression, anxiety and post-traumatic stress, etc. Violent crime leads to negative schemas resulting in chronic depression (Janoff-Bulman, 1992; Roth & Newman, 1991). A study found that victims of violent crime exhibited acute stress disorder (19%) and PTSD (20%) symptoms when they were interviewed within one month of the event (Breslau et al., 1991). In addition, in Shalev et al. (1996), a study of trauma survivors found that 25% of the survivors developed PTSD (Shalev et al., 1998). A national study of psychiatric disorders in New Zealand prisons demonstrated the prevalence rates for PTSD of female prisoners 16.6% and 9.5% and 8.5% in remanded and sentenced male prisoners (Brinded et al., 2001). Thus crime can lead to stress and related mental disorders and this is a vicious cycle. However, on the other hand in certain situations crime can also occur in the absences of stress. This is based on the pleasure hypothesis to commit crime especially in dissocial personality disorder. Hence, all people under stress do not commit crime only few individuals with high risk are prone to commit crime.

## **TREATMENT IMPLICATIONS**

1. Prevention of ACEs like abuse and neglect of children.
2. Promote resilience: One should promote resilience in the children by one single factor, by forming a stable relationship with the parent or caregiver.
3. Family engagement: The family needs to engage with children and teach them self-regulatory skills to improve emotional regulation.
4. Promote healthy coping mechanisms in children.

## CONCLUSIONS

Stress in childhood can lead to neurodevelopmental (chemical, structural, molecular) changes in the brain, and the interplay of behavioral, environmental, and genetic factors lead to different coping mechanisms and few develop aggression and impulsivity, which predicts adolescent behaviors like deviant peer imitation/substance use/mental illness which strongly predicts crime. Crime can, in-turn, lead to stress and related disorders, which can increase the crime further and it is a continuing vicious cycle. It keeps passing on to generations strengthening the cycle of violence. This vicious cycle needs to be cut at an earlier stage where the children need to be protected from the ACEs and improve the protective factors like trusted adult and parenting, positive attitudes, good social skills, etc.

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## Part V

# MANAGEMENT OF STRESS



*The specific management of each disorder, wherever applicable, is dealt with in the corresponding chapter in the previous parts. In this part V, the book focuses on the broader management of stress – such as availability of drugs (examples some evidence to suggest that Anti-depressants act as Anti-stress agents), psychological treatment, traditional methods of stress management, the role of psychological first aid in stress alleviation especially in community level, and preventive aspects. The transformational growth of telepsychiatry during this COVID-19 pandemic led us to add a chapter on stress and tele-psychiatry focused on its various delivery models of stress management.*

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<b>33</b>	<b>Psychological treatment of stress</b> <i>Supriya Dastidar, Bettahalasoor Somashekhar, Ashok Kumar Jainer</i>
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## **PSYCHOPHARMACOLOGICAL MANAGEMENT OF STRESS AND RELATED DISORDERS**

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### **OUTLINE**

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| 5. PHARMACOLOGICAL MANAGEMENT OF STRESS RELATED ILLNESSES | 6. CONCLUSIONS  |

## **INTRODUCTION:**

Stress plays a significant role in the etiopathogenesis of most of the psychiatric disorders. Broadly, stress may be physical, physiological, psychological, or oxidative. Stress may be acute or chronic and persisting (Rohleder, 2019). The pathological response and adaptation to such acute or chronic stressful events are conceptualised as etiopathogenesis underlying common psychiatric disorders (Hammen et al., 2009). Balance between the stress vulnerability at one end and the resilience of the individual at the other determines the direction of the outcome. Achieving this balance is not simple and it is purely dependent on the nature of the stress and responder's characteristics. Hence the effect of stress and its response

hugely varies and the experience of stress is relatively personal (Fothergill et al., 2004). Stress is universal and at the same time quite personal. Events that are novel, unpredictable, that poses a threat to the individual's ego and a sense of control produce significant stress. Resilience primarily reflects the cognitive flexibility and adaptability of an individual that helps to overcome the adversity. Early life experiences, internal capacities and external support play a major role in shaping one's ability to respond to stress (resilience) (Friedberg & Malefakis, 2018). Acute and chronic stress of varying degrees is postulated in the evolution and persistence of psychiatric disorders like anxiety, depression, post-traumatic stress disorder, substance use and dementia. Stress may be conceptualised as a predisposing, precipitating, triggering, contributing or perpetuating factor in the pathophysiology of mental illness. Additionally, stress plays a role in physical conditions such as hypertension, gastric ulcer, bronchial asthma, obesity, inflammatory conditions and cardiovascular disorders (Cassel, 2017). Overactive amygdala, hypofunctioning prefrontal cortex and the associated neurohumoral cascade lead to neurocircuitary changes in response to stress. Neuroendocrine, inflammatory, epigenetic and neuroplasticity related mechanisms underlie the development of neuroadaptation and stress response (McEwen et al., 2015).

Non-pharmacological measures such as balanced diet, physical activity, sleep hygiene and more commonly substance abuse are practiced to reduce stress. It has been noted in history, that various indigenous herbs, potions, concoctions and substances were used by humans to relieve stress. Medications, different forms of psychological therapies and neurostimulation techniques are also available for stress management. In this chapter, the authors discuss the psychopharmacological management of stress.

## **STRESS RESPONSE MECHANISMS AND POSSIBLE DRUG TARGETS:**

Understanding the neurobiology of stress and mechanisms involved in the pathological effects of stress may shed light on the possible pharmacological targets. Hormonal and neuroendocrine changes are common during stress related events. Stress precipitates secretion of Norepinephrine (NE) and corticotrophin releasing factor (CRF). CRF leads to hypothalamo-pituitary-adrenal (HPA) axis activation. Endogenous opioids, endocannabinoids, brain derived neurotropic factor (BDNF) and neuropeptide-Y(NPY) act as naturally occurring anti-stress agents

and attempt to counterbalance the effects of CRF (Valentino & Van Bockstaele, 2015; Wyrofsky et al., 2019). Maladaptive up regulation of NE, CRF and down regulation of NPY are shown to be associated with PTSD (Osório et al., 2016). Chronic mild stress (CMS) model is a well-researched animal model for depression. CMS leads to a variety of neurochemical and neurocircuitary changes that leads to behavioural changes such as low mood and anhedonia. Epigenetic modifications such as histone de-acetylation and deoxyribonucleic acid (DNA) methylation are reported consequences of stress. De-acetylated histones lead to poor transcription of genes and ultimately poor neuroplasticity (Sun et al., 2013). Individuals with specific genetic allelic variations in the serotonin transporter gene (5HTLLPR) and BDNF gene are at a higher predisposition to develop common psychiatric conditions subsequent to stress/adversity (Nestor et al., 2019). Additionally, sleep disturbances following acute stress, especially rapid eye movement (REM) sleep dysregulation is implicated in the development and progression of post-traumatic stress disorder. Nightmare, a cardinal symptom in PTSD is primarily REM sleep disturbance (Repantis et al., 2020). REM sleep modulating agents might prove beneficial in altering the progression of stress related disorders. Agents that promote neuroplasticity may be of particular interest in the management of stress, anxiety and depression. Acquisition, consolidation, re-consolidation of memories and synaptic dysconnectivity are the cognitive changes underlying post-traumatic stress disorder. Drugs targeting such memory re-consolidation and synaptic connectivity may prove to be beneficial in PTSD (Abdallah et al., 2019). Oxytocin levels are shown to be associated with prosocial behaviours such as trust, empathy and generosity. Through its interactions with other hormonal levels especially cortisol, oxytocin may play a crucial role in attenuating the negative effects of acute stress. The potential role of neuroactive steroids is considered in the management of anxiety and depression recently. The gut-microbiota-brain axis has a key role in regulating the stress response, immunity and neuroinflammation (Rea et al., 2016). In inflammatory conditions, animal studies show probiotics may play a crucial role in stabilizing the HPA axis and brain neurotropic factors.

### **ACUTE VERSUS CHRONIC STRESS:**

The response of the individual depends upon their resilience as well as the characteristics of the stress. Stress may be acute or chronic. Acute stress usually represents ‘on the spot’ or immediate stressful situation. Examples of acute stress; going on a stage to give a speech, visiting a lab for blood test, exams, waiting in a long queue or traffic jam, an accident etc.., Acute stress is usually endured

with autonomic arousal. As in the first instance, going on a stage to give a speech, symptoms of autonomic arousal include tremors in hands, palpitations, sweaty palms, increased respiration, dizziness, change in voice and so on. Such an arousal leads to sharpening of cognitive and muscular activity and may help in successfully enduring and overcoming the stressful event. Also, in predisposed individuals, such acute stress may be overwhelming and the attendant response may either make them endure the event with considerable difficulty/tension or may induce extreme anxiety and thereby avoidance. Both responses are maladaptive and repeated such events may lead the individual to develop negative coping mechanisms like avoidance (Hammen et al., 2009).

Chronic stress, on the other hand, may result from persistent low level or repetitive high level stressors in an individuals' life. Examples of low level persistent stress include poverty, unemployment and chronic medical conditions. Examples of repetitive high level stressors include domestic violence, childhood sexual abuse and job related deadlines. Generally, the human stress response system has evolved to attend to stressors of acute nature. Physiologic response and adaptation to chronic stress is much less understood (Rohleder, 2019). Persistent stressors induce prolonged repercussions that are long-lasting and unfortunately animal models could not replicate such stress reverberations. Chronic stress triggers persistent activation of the stress response, neuroendocrine system which ultimately leads to maladaptive cortisol secretion and its effects on multiple organs including nervous system (Lee et al., 2015). Chronic activation of stress systems also leads to persistent effects on neuronal firing and epigenetic modifications (Hunter et al., 2009; Rohan Walker et al., 2013). Again the varied definitions used for chronic stress such as chronic mild stress (CMS), chronic unpredictable stress (CUS), Chronic unpredictable mild stress (CUMS) and chronic variable stress (CVS) has impaired the progress in the field.

## **CLINICAL SYNDROMES RELATED TO STRESS:**

Stress is prevalent and multidimensional. Intrinsic factors such as genes and temperament, extrinsic factors such as family and social support along with the nature and severity of the stressor determines the coping behaviour or stress response. Resiliency of the given individual has been postulated as the underlying mechanism for the varied manifestations of similar stress in a given population. Resiliency as a concept is difficult to be emulated in animal models and hampered research in this area. Sub-syndromal mental health concerns are common reactions

following stress. However, in a sizable minority stress may be associated with the evolution of psychiatric disorders (Hammen et al., 2009). Current diagnostic systems classified them separately under “Trauma and stress related disorders” (DSM-5) and “Disorders associated with stress” (ICD-11). All these disorders mandate the presence of stressor as a necessary (but not sufficient) condition for the development and manifestations of the illnesses. The stress related manifestation may present in one of the following ways;

1. Individuals may present to clinic with features which meet the diagnostic threshold for a clinical syndrome defined by the contemporary classificatory system where stress is specified. In other words, the stress is an essential criterion for the diagnosis. They include acute stress disorder, adjustment disorder, PTSD, reactive psychosis, somatoform disorders and dissociative disorders. The management of these disorders are covered in detail under Part II of the book. However, a brief overview of pharmacological interventions for acute stress disorder, adjustment disorder, PTSD, reactive psychosis is presented here.
2. Stress precipitates a well-defined disorder but not necessarily cause the illness – In other words stress is not essential criteria for a diagnosis, however stress does play role in the several aspects of these illnesses such as onset, progress, treatment response and prognosis. The management of these disorders is covered in part III of the book.
3. Stress results in subsyndromal clinical presentation either due to short duration or milder severity. However, the symptoms cause suffering or significant impairment in functioning or both. Such presentations are usually in the background of immediate and obvious psychological or social stressors such as performance (exam, public speaking, attending an interview), medical procedure, etc. They are usually not treated or offered only psychological treatment as they are overall clinically understandable and are short lived. Although the pharmacological management of such presentation are not systematically carried out, clinical experience suggests that individuals with subsyndromal presentation benefit from pharmacological treatment. The treatment is usually short term and symptomatic. We have covered these groups of presentation in subsequent sections.

In the following section, two aspect of pharmacological treatment are provided. First a brief overview of pharmacological intervention for trauma and stress related disorders (DSM-5) and disorders associated with stress (ICD 11) and second, potential pharmacological agents useful in symptomatic treatment of stress irrespective of the diagnosis or when the symptoms do not meet diagnostic criteria for a specific disorder.

## **PHARMACOLOGICAL MANAGEMENT OF STRESS RELATED ILLNESSES**

### **Acute Stress Disorder:**

The evidence is poor with respect to pharmacological interventions and certain regulatory guidelines (Forbes et al., 2007) are against the use of pharmacological agents in acute stress. Benzodiazepines are suggested only in the instances of extreme, overwhelming anxiety leading to panic and dysfunction. Such benzodiazepines use is limited and usually given only for a few days. The pharmacological interventions studied are mostly in the context of preventing the progression towards post-traumatic stress disorder. Hydrocortisone has shown promise in preventing PTSD when administered shortly after trauma. Other agents like propranolol, morphine, benzodiazepine and atypical antipsychotics are shown to be generally ineffective.

### **Adjustment Disorder:**

With the transient and self-limiting nature of the illness, mostly psychological interventions were utilized. Controlled pharmacological trials are limited and have significant methodological issues. Low to moderate quality evidence suggests Selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, tianeptine and trazodone when used either alone or in combination with psychological interventions had proved to be useful in the management of adjustment disorder (O'Donnell et al., 2018). A non-benzodiazepine anxiolytic etifoxine (dose 150-200mg/day) is reported to be efficacious in controlled studies (Stein, 2018).

### **Post-Traumatic Stress Disorder (Ptsd):**

Pharmacological management of PTSD involves two strategies namely; prevention and treatment. Prevention strategy involves using drugs immediately following the trauma to prevent the development of PTSD. Psychological interventions were superior to pharmacological ones in preventing the development of PTSD (Shalev et al., 2012). Hydrocortisone, beta-adrenergic blockers, benzodiazepines,

morphine, low dose antipsychotics and SSRIs are used as prophylactic agents. Except hydrocortisone, efficacy of the other agents is not proven conclusively as prophylactic agents (Thomas & Stein, 2017; Astill Wright et al., 2019). In fact, benzodiazepines actually accentuated the risk of PTSD symptoms development and hence are not recommended as a preventive agent (Qi et al., 2016). Use of hydrocortisone is also marred by problematic side effects, poor standardization of dose and duration of therapy but is definitely an interesting area for further research. As treatment options, SSRIs like paroxetine, sertraline and noradrenergic agents like venlafaxine are considered as first line agents. The effect size of these agents is small and nearly one-third of patients do not respond to these medicines. A recent network meta-analysis suggested desipramine, fluoxetine, paroxetine, phenelzine, risperidone, sertraline and venlafaxine were better than placebo in the management of PTSD (Cipriani et al., 2018). Preliminary evidence supports the use of sub-anaesthetic dose of ketamine as a novel agent in treating chronic PTSD. In a randomised trial, single infusion of ketamine was shown to effectively and rapidly attenuate the PTSD symptoms (Feder et al., 2020). Further replication of the positive results is necessary before routine utilization of ketamine in clinical practice.

### **Reactive Psychosis:**

In a relatively small proportion of individuals, acute stress may trigger psychotic symptoms such as delusions and hallucinations. Classically, they are called as reactive psychosis or psychogenic psychosis. The illness responds well to treatment and usually carries a good prognosis. Common presentations are religious or somatic delusions, agitation and suicidality with/without auditory verbal hallucinations (Chavan & Kulhara, 1988). However, the interest in research in this area is dwindling since two decades. Recent viral pandemic had again brought the attention of professionals due the unique nature of this syndrome. Fear of contracting a deadly viral illness, deranged daily routine along with the social restrictions implemented to contain the spread of the infection had placed undue stress on the general public (D'Agostino et al., 2020). Importantly, poor social support added to the stress may precipitate the psychotic illness. Older age, cognitive decline, disturbances in sensory functions and social isolation may play a crucial role in the etiopathogenesis. Most patients respond to low dose antipsychotic treatment within few days (Valdes-Florido et al., 2020). This syndrome has a relatively poor diagnostic stability over time and mixed results with respect to relapse of psychotic phenomena.

**Pharmacological Agents Useful In Symptomatic Treatment Of Stress:**

There is a tendency among health professionals to offer differential treatment based on the presumptive causation such as psychological or biological. However, a distinction between biological and psychological stress is futile because what is psychological is ultimately biological. It is well known that psychological or social factors play role in several physical and psychiatric illnesses but they are primarily treated with drugs. Therefore there is a definite place for judicious use of psychotropic drugs in stress induced symptoms even if they do not meet criteria for a diagnosis according to classificatory system. In the following section, we have attempted to provide rational for the use of different group of drugs in stress manifestations.

**Serotonergic Agents:**

Depletion or reduction in brain serotonin levels is associated with anxiety like behaviour. Selective serotonin reuptake inhibitors (SSRIs) like fluoxetine increase the availability of serotonin in the synaptic junction and are shown reduce the hyperactivity of amygdala and promote neuroplasticity. Serotonergic agents are helpful in reversing the behavioural manifestations of chronic mild stress (CMS) in laboratory conditions (Willner, 2017). Through their influences on protein kinases and second messengers, SSRIs on chronic administration potentiate the gene expression of neurotropic factors and ultimately adaptive neuroplasticity. SSRIs like sertraline and paroxetine are approved for PTSD. Meta-analytic evidence supports the use of SSRIs like fluoxetine, paroxetine and noradrenergic agents like venlafaxine in the management of PTSD (Hoskins et al., 2015). Monoamine oxidase inhibitors and tricyclic antidepressants use are limited by their side effects. However, these serotonergic agents exhibit delayed onset of action which may not be favourable during acute stress.

Psychedelic drugs such as psilocybin, lysergic acid diethylamide (LSD) and 3, 4 methylenedioxy methamphetamine (MDMA) are researched with renewed interest to assist during therapy sessions for depression, anxiety and post-traumatic stress disorder (PTSD). The existing first line serotonergic agents are criticized for delayed onset of action, need for longer continuation therapy and being ineffective in 30-40% of patients. Psychedelics, on the other hand are reported to produce meaningful reduction of distress and long-lasting effects within few supervised sessions (Muttoni et al., 2019). However, further systematic research evidence is necessary before routine clinical use of psychedelic drugs.

**Gamma Amino Butyric Acid (Gaba-Ergic) Agents:**

Benzodiazepines play a crucial role in ameliorating acute stress. Owing to addictive potential and effects on cognition, their use is suggested to be only for short term and kept minimal. Neither SSRI nor benzodiazepine administered within 3months following a trauma, has been shown to be effective in preventing the evolution of PTSD (Astill Wright et al., 2019). Endogenous steroids are studied with avid interest as novel agents in the management of anxiety and depression. These neurosteroids are mainly corticosteroids, estrogen related steroids and positive allosteric modulators (PAM) of GABA-A receptors (Rasmussen et al., 2017). GABA-ergic steroids are active at both synaptic (phasic) and extrasynaptic (tonic) sites and thereby are more efficacious and different from benzodiazepines which are active mainly at synaptic sites (Zorumski et al., 2019). Neurosteroids are shown to possess anxiolytic, sedative, analgesic, anticonvulsive and anaesthetic properties at different doses (Belelli et al., 2020). Brexanolone (Allopregnanolone), a neurosteroid, a congener of progesterone is recently approved by Food and Drug Administration (FDA-USA) for the management of post-partum depression. Given intravenous over sixty hours, Brexanolone has been shown to be fast and effective in improving mood and the effect lasted for 30 days after single infusion (Meltzer-Brody & Kanes, 2020). Orally active neurosteroid SGE-217 (Zuranolone) has shown initial promise in clinical trials to relieve depression in both men and women.

**Noradrenergic agents:**

Noradrenergic reuptake inhibitors like venlafaxine and reboxetine are used as well for different anxiety disorders. Reconsolidation of already existing memories help to mitigate the painful memories associated with trauma and related disorders. Alpha adrenergic blockers like clonidine and guanfacine are also utilised to prevent fear memory consolidation albeit poor clinical efficacy. Another alpha adrenergic blocker, prazosin, decreases noradrenergic hyperactivity and thereby facilitates sleep and reduction of nightmares. Sleep disturbances and nightmares in PTSD are independent risk factors for suicide. Prazosin is used off-label to reduce nightmares in PTSD (Waltman et al., 2018).

**Beta-blockers:**

Propranolol is a non-selective beta adrenergic antagonist. This molecule is postulated to interfere with the fear consolidation following trauma. Propranolol blocks the post-synaptic adrenergic receptors in basolateral amygdale, thereby

interfering with the consolidation of fear memories. Propranolol, usually given at 40 mg dose has been reported to be effective during the reconsolidation phase of memory in pre-clinical studies (Bolsoni & Zuardi, 2019). However clinical studies used it in preventing the evolution of PTSD following trauma failed to produce consistent results. Propranolol is still used in specific performance anxiety related events to prevent or reduce the peripheral manifestations of stress and anxiety.

### **Glutamatergic agents:**

Glutamatergic drugs like ketamine are tried in relieving the manifestations of treatment resistant anxiety, depression and PTSD. Ketamine, a non-competitive N-Methyl D-Aspartate (NMDA) receptor blocker, enhances glutamatergic neurotransmission and regulates gene expressions and neuroplasticity (Feder et al., 2014). Single sub-anaesthetic dose of ketamine infusion over 40 minutes had shown rapid antidepressant response within 24 hours that lasts up to 2 weeks. Repeated infusions are currently tried to maintain the efficacy. Subset of depressed individuals with anxiety features are shown to benefit more from ketamine infusions (Abdallah et al., 2019). Another glutamatergic drug, D-Cycloserine in conjunction with psychotherapy (exposure based) has been shown to be effective in PTSD and other anxiety disorders (Ragen et al., 2015). Drugs targeting the metabotropic glutamate receptors (mGLU2/3 agonists) are found to be anxiolytic in animal studies.

### **Endocannabinoids:**

Dysfunctional endocannabinoids signalling and an increase in CB-1 receptors brain has been shown to be associated with hyperarousal and increased threat perception in PTSD. Endocannabinoids act as tonic gatekeeper against stress by modulating the HPA axis (Ney et al., 2019). Endocannabinoid signal enhancement may influence memory consolidation, retrieval and extinction. Both preclinical and clinical studies demonstrated the role the cannabidiol and cannabinoid (CB-1) receptor agonists (ex-Nabilone) to reduce anxiety, depressive and PTSD symptoms but with mixed results (Ney et al., 2019). Endocannabinoids regulate the Locus Ceruleus – Noradrenergic system tone and adaptability during stress (Wyrofsky et al., 2019). Cannabinoids are shown to improve sleep quality and reduce hyperarousal and nightmares in PTSD. However, there is currently only limited evidence of cannabinoids use in psychiatric disorders (Bonaccorso et al., 2019).

**Opioids:**

The release of endorphins in amygdale following acute stress assists in coping with the stressful situations and reduces the emotional and physical pain. Individuals with PTSD exhibit high co-morbid pain related conditions. Therapeutic modulation of opioid signalling may be useful in reducing stress and anxiety. Morphine, a mu opioid receptor agonist, is shown to attenuate acute stress response and potentiate adaptation in animal models. Morphine is also linked with retrograde amnesia for contextual conditioned fear in animal models. The use of morphine in reducing the progression of PTSD is studied with mixed results (Thomas & Stein, 2017). The timing of the morphine injection following the trauma may influence the outcome (RaiseAbdullahi et al., 2019). Kappa opioid receptor antagonists have shown early promise as anxiolytics and antidepressants in preclinical studies.

**Other agents:**

Antipsychotics like risperidone, quetiapine and olanzapine are used at lower doses as adjunct treatment options in people with resistant stress related disorders and also for sleep disturbances. Risperidone and olanzapine either as monotherapy or augmentation is supported with clinical evidence for the use in resistant chronic PTSD. Quetiapine, on the other hand, has beneficial effects against uncomplicated generalised anxiety disorder (Albert et al., 2016). Oxytocin is a neuropeptide hormone involved in the regulation of prosocial behaviours and emotional attachment. Intranasal oxytocin administration may be effective in fear extinction and fear conditioning (Thomas & Stein, 2017). Histone deacetylase inhibitors (Ex: Valproate), Promoters of histone acetylation may facilitate adequate gene expression and neuroplasticity. L-acetyl carnitine is a naturally available substance that promotes acetylation of histones. Neuropeptide-Y(NPY) physiologically regulate feeding, reproduction, energy homeostasis and memory. In animal models, following chronic variable stress, NPY levels in Amygdala were reportedly low. However, in stress resilient animals, the NPY levels did not reduce (Kautz et al., 2017). NPY and vasopressin system drugs are currently researched in different preclinical studies to relieve anxiety and depression (Sartori & Singewald, 2019). Other agents like buspirone (5-HT1-agonist), agomelatine (melatonergic agonist) (Willner, 2017), and CRF receptor antagonists (Carrasco & Van de Kar, 2003) are to be explored further.

**Nutraceuticals and supplements:**

Nutraceutical agents like N-Acetyl Cysteine (NAC)(Harvey & Shahid, 2012), omega-3-fatty acids, s-Adenosyl methionine, ascorbic acid, and curcumin are explored in relieving stress and related disorders (Willner, 2017). Omega -3 fatty acids supplementation may help in clearing fear memory and promote hippocampal neurogenesis thereby reducing the PTSD symptomatology (Thomas & Stein, 2017). Probiotic supplements effectively boost the stress resilience and improve the information and emotional processing in healthy and depressed individuals. The central anti-inflammatory effects of minocycline, a tetracycline antibiotic are suggested secondary to gut microbiome regulation (Rea et al., 2016). The role of probiotics in preventing stress induced damage to neurocognition is recognised recently (Papalini et al., 2019).

**Highlights:**

- Stress plays a significant role in the etiopathogenesis of most psychiatric disorders.
- Acute and chronic stress of varying degrees is postulated in the evolution and persistence of psychiatric disorders such as anxiety, depression, post-traumatic stress disorder, substance use and dementia.
- Neuroendocrine, inflammatory, neuroplasticity and epigenetic related mechanisms underlie the development of neuroadaptation and stress response.
- Understanding the neurobiology of stress response might shed light on potential molecular targets for pharmacological management of stress and related disorders
- Serotonergic, noradrenergic, GABA-ergic, glutamatergic, endocannabinoid, opioid and other novel agents that are utilised in the stress management are outline in this chapter

**CONCLUSIONS**

There is an exponential increase in the research on pharmacological intervention for stress. However, the wealth of research has not meaningfully identified any pharmacological agent that is specifically effective as ‘anti stress drug’. The pharmacological management essentially remain symptomatic and are extrapolated from effectiveness of pharmacological agents in other established psychiatric syndromes. Although several studies exclusively focused on PTSD, the current pharmacological interventions for PTSD also remain symptomatic. Factors such as variable definitions of stress, incomplete understandings of effects of stress on body

and mind and lack of reliable biological measurements of stress have contributed poor clinical utility of the research. Despite limitations, evidence suggests that pharmacological agents provide symptomatic relief to stress manifestations. Hence pharmacological treatment is justifiable at least in short term, even when the clinical features do not meet diagnostic threshold for established stress related disorders.

It has been postulated that maladaptive responses to stress are secondary to poor neuroadaptation and neuroplasticity. Therefore, future studies should aim at developing pharmacological agents which enhance neuroadaptation and promote neuroplasticity, while continue exploring effectiveness of pharmacological agents based on the clinical syndromes.

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## **PSYCHOLOGICAL TREATMENT OF STRESS**

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### **OUTLINE**

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| 1. NEED FOR PSYCHOLOGICAL THERAPIES              | 2. HISTORY OF PSYCHOLOGICAL THERAPY FOR STRESS    |
| 3. GENERAL PRINCIPLES OF PSYCHOLOGICAL TREATMENT | 4. SELECTION OF PSYCHOLOGICAL THERAPIES           |
| 5. PREVENTION OF STRESS                          | 6. STRESS MANAGEMENT FOR HEALTHCARE PROFESSIONALS |
| 7. MEASUREMENT OF EFFECTIVENESS OF THERAPY       | 8. CONCLUSIONS                                    |

Pharmacological treatments for stress and stress related disorders has been described in earlier chapter. While these have shown benefits and are the treatments of choice for short term stress, psychological therapies are still preferred for long term management. People with maladaptive personality traits which cause them psychological distress in difficult situations have found good benefit from talking therapies. In most instances however, psychological therapies are combined with medical treatment for optimal effect.

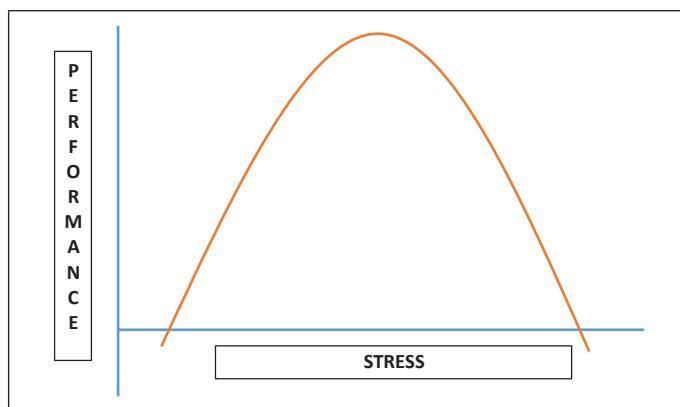
### **NEED FOR PSYCHOLOGICAL THERAPIES**

Stress is not always counter-productive. Some amount of stress, called as Positive stress or Eustress provides the energy and tools needed to find and execute solutions. Stress can help us to stay alert, work harder and improve our reaction times. For example, performing well at exams, interviews, and competitions; staying alert

in busy and fast-moving traffic and during potentially dangerous activities like mountain climbing.

However, when stress becomes continuous, intense or long-lasting, it can cause fatigue, be perceived as distressing and negatively impact on performance. It is well known that performance improves with increasing the severity of stress to a point, it reaches a peak and then performance decreases with further increase in severity. It is well known that, when severity of stress is plotted along the x-axis and performance along the y-axis, we get an inverted-U shaped curve as shown below in Figure 1.

Figure 1: Stress vs Performance Curve



Excessive stress adversely affects physical and mental health and cause symptoms such as headaches, insomnia, high blood pressure and anxiety. Long-standing stress has been negatively implicated in chronic illnesses such as acid-peptic disease, cardiac problems, diabetes and obesity. Stress has been implicated in onset and maintenance of several mental illness. Early and effective management of stress not only improves the physical and mental health of the individual, but it also enhances their quality of life. It helps people feel in control of their lives in order to attend to their own needs and life goals and thus derive better satisfaction from life (Harter et al., 2003).

### HISTORY OF PSYCHOLOGICAL THERAPY FOR STRESS

The importance of healing people of stress has been acknowledged since time immemorial by civilisations across the world. Some of the current concepts in

psychological therapies find their roots in the ancient practices of healing and meditation like *Yoga* and *Dhyana* (Indian meditation practices), *Qigong* (Chinese healing technique) (Cohen, 2000) and *Zazen* (Japanese Zen Buddhist practice). The oldest written material about meditation can be found in the *Vedas* which are the ancient religious texts of India.

The Healing temples in Ancient Greece called *Asclepions* (Ergill, 1997) were originally constructed to worship *Asclepius*, were also the first ‘hospitals’ of western civilisations. The Greeks believed that disease was a result of not just bodily injury but also the upshot of complex interactions between social, environmental, spiritual, physical and emotional factors. Physicians in these hospitals believed in a holistic approach to treat patients, including providing psychotherapy, herbal remedies, treatments and surgeries, most of which were prescribed depending on the dreams that the patients experienced.

Modern psychological therapies for stress combine both traditional healing practices and more recent works on psychoanalysis, cognitive psychology and behavioural therapy. The American psychologist, Carl Rogers coined the term ‘Counselling’ which is now commonly used to describe low intensity talking therapies; while the term ‘Psychotherapy’ denotes more structured and longer-term work. These terms however are not used in the strictest sense of meaning which will become more obvious as we read further.

## **GENERAL PRINCIPLES OF PSYCHOLOGICAL TREATMENT**

In order to effectively manage stress, it is important to first understand the various dimensions of stress. Stress can be examined under several factors including individual health and well-being, socio-cultural differences and psychological factors. It can be described under the following three main elements. Although they are described separately in reality, it is the product of a unique combination of and complex interaction between all three:

### **a) Stimulus**

The impetus for stress (Stressor) can either arise within the person (hunger, sex etc.) or be an external stressor (natural disasters like pandemics, wars, major changes in life, everyday challenges and work pressures). A stimulus is a prerequisite for stress, although its impact on an individual depends on the below two factors.

**b) Individual characteristics**

A person's personality, resilience, coping skills and the resources available to him (family and social support, employment and finances) play a major role in the development, experience and expression of stress. For the same reason, these entities also offer ample potential for effective interventions as described further in this chapter.

**c) Consequence**

Consequences of stress can be in one or more the following

1. Stress related psychiatric syndromes

Stress can cause a range of symptoms which together meet the diagnostic criteria for specific mental illnesses such as acute stress reaction, PTSD, adjustment disorders, reactive psychosis, somatoform disorders and dissociative disorders. They are categorised as "Trauma and Stress related disorders" in DSM-5 (American Psychiatric Association, 2013) and "Disorders associated with stress" in ICD-11 (WHO, 2020). These are a direct result of stress and are addressed as such in Part II of this book.

2. Disorders precipitated or maintained by stress

In illnesses such as depression, bipolar disorder, psychoses etc., stress plays a role in triggering and/or maintaining the illness; or even leads to a relapse. Management of stress in such cases might not necessarily treat the mental disorder but improves patient engagement, expedites treatment and remission, and promotes recovery. This is discussed in detail in Part III of this book.

3. Physical health consequences of stress

Stress has been implicated as a cause of several chronic physical illnesses such as hypertension, heart disease, stroke, obesity etc. The relationship between stress and physical disorders is explained in more detail in Chapter 9. In addition, negative coping methods like over-eating, smoking and alcohol consumption can indirectly cause detrimental impact on health and well-being.

4. 'Sub-syndromal'

In these cases, stress is not severe enough to meet the criteria for any

specific mental illness but is nevertheless distressing to the client. It can have a wider impact on the society by weakening the family structure, work-place absenteeism, and decreased productivity in general. These issues are best addressed through psychological therapies of varying intensities tailored to the individual. Stress of this nature is explained further in this chapter.

**Figure 2: Multi-dimensional aspect of Stress**



### **Assessment of Patient characteristics**

Assessment of patient characteristic for therapy is helpful in selecting appropriate therapy for a given patient. Under comparable environmental and social-ecological conditions, there are individual differences in how people respond to stress which could be related to their personalities, motivation, cognitive appraisal, defences and coping styles. Thus, the intensity of psychological stress one experiences is largely determined by whether the environment is perceived as dangerous, troublesome, uncontrollable or deleterious to their well-being.

A person's personality has an influence on how he or she appraises and copes with stressful situation. It also affects the selection and shaping of the situation. Certain characteristics make people more resilient to stress and they thus cope better than others. Some of these characteristics are (Bartlett, 1998):

- Awareness of one's own self, strengths and weaknesses
- Optimism, Hope and Self-efficacy

- Sense of Coherence
- Hardiness and internal locus of control
- Nurturing a variety interests, hobbies and problem-solving and coping skills
- Being proactive and productive
- Having good communication and relationship skills

Psychological therapies try to introduce or boost these features while aiming to control the cognitive, emotional and social aspects of stress. They also target the underlying causes of stress which are different for different people in their own unique situations and even vary with time. Thus, the specific therapy needs to be chosen and further tailored to the condition which results from the permutation and combination of all these three entities.

A formal assessment by a trained therapist is fundamental to uncover this and usually precedes any treatment plan. It also provides a good opportunity to build a rapport with the patient and assess the suitability for therapy in general. A baseline scoring of severity of stress can also be done using self-report questionnaires and various tools such as Social Readjustment Rating Scale (SSRS) (Holmes, 1967) and Perceived Stress Scale (PSS) (Cohen, 1983). If suitable, the therapist then proceeds to choose the most appropriate modality for the patient.

## **SELECTION OF PSYCHOLOGICAL THERAPIES**

We find it useful classify several therapies used in the management of stress consequences broadly into four groups based on specific characterises of therapy and needs of the client. The grouping is pragmatic and has clinically utility. The following factors are taken into consideration while grouping.

- Easy to use
- More meaningful in terms of options available for a specific client profile
- Clarity regarding duration and frequency of the sessions
- Expected outcomes such as symptomatic relief to modification in personality traits
- Helps the clinician tailor the therapy to the needs and characteristics of the individual

Although the principles and techniques of therapies overlap, grouping them has clinical utility in selecting appropriate therapy for the given individual and to ensure judicious use of limited resources.

For quick reference, a summary of various psychological therapies is given in Table 1.

### **I. Self-help Interventions:**

These are designed for people who are psychologically well adjusted and have an intact ego; but are experiencing some ongoing crises. The stressor is usually external and of short duration. The goal is to reinforce self-motivation and support clients to use their own internal coping mechanisms along with specific advice, logistic help and social support. These therapies offer practical and emotional support, provide an opportunity for catharsis (emotional release) and guide problem solving discussions with an aim to re-establish normal level of functioning.

Self-help interventions for stress are beneficial and generally adequate for people who are well-adjusted, not suffering from severe mental illness and psychologically minded but experiencing major life changes, changes in role, bereavement, financial losses, relationship breakdown etc. in addition to managing stress, they may also help in improving one's ability to become objective and solve problems.

It can be delivered in two forms:

#### **Self-help literature:**

These are designed to be used by people themselves in their own time. It is most useful for those with mild stress with minimal or no functional impairment and relies heavily on self-motivation and intellectual abilities. Some examples are:

1. Guided self-help books
2. Online courses like computerised CBT
3. Mental health apps
4. Support groups in the community or online

### **Counselling:**

Counselling uses many non-specific concepts and techniques of psychotherapy to tailor the intervention to the requirements of the client and the expertise of the counsellor. These include but are not limited to providing information, catharsis and cognitive restructuring. Some examples of counselling are as follows:

1. Problem-solving counselling- is used when the stress is related to life circumstances.
2. Interpersonal counselling- is used when the stress is due to relationship problems in family or work settings.
3. Debriefing- is used for survivors of disasters.
4. Grief counselling- works through stages of grief and advises about practical issues related to the loss of person.
5. Counselling for students- who are experiencing adjustment difficulties and stress of university life

## **II. Supportive Psychological therapies**

Patients with diagnosable mental health conditions commonly suffer from stress related to their mental illnesses. Apart from social and financial support, they benefit immensely from mobilising their internal coping resources through supportive psychological therapies. The aim of supportive approach is to empower the clients to utilise their own inner resources and mobilise all possible external resources to cope with the demanding situation. There is no rigid application of formal theoretical model. They are based on the general principles of psychotherapy namely person-centred approach, good therapeutic alliance, empathy, unconditional positive regard, non-judgemental attitude, providing information, catharsis, and encouraging hope, positive-thinking and self-help.

Supportive psychological therapies can be delivered by psychiatrists, psychotherapists, counsellors, or even clinicians from different backgrounds with training in a specified area or under the supervision of a trained therapist. These can be given in individual, couple or group settings. They are best suited for people who have mild-moderate stress with mild functional impairment and have a stable personality.

Some examples are given below:

### **Coping Strategies:**

Some of the coping methods (Lazarus, 1984) that can be taught and reinforced are as mentioned below:

**Problem-centred coping:** These methods aim to identify the problem and control the stressful situation by using practical and pragmatic ways to manage it. Methods used are:

- Problem solving skills
- Time management
- Planning and prioritisation of work

**Emotion-focussed coping:** Emotion-focused coping is a type of stress management approach that attempts to reduce negative emotional responses associated with stress. Emotion-focused techniques might be the only realistic option when the source of stress is beyond individual's control. For example, anxiety related to role change, loss or grief etc.

Some examples of positive coping methods are distraction techniques, emotional disclosure by talking or writing journals, prayer and meditation, mindfulness-based activities and cognitive reappraisal (described below).

Practising these skills have shown to reduce or counter the use of negative coping methods like over-eating or comfort eating, consuming alcohol or non-prescription drugs etc. which are potentially harmful to health and well-being.

**Social interventions:** People can be signposted to specific support groups in the community which meet regularly to participate in events and activities aimed to improve well-being. Attending and being involved in these groups improves people's confidence and instils a sense of responsibility by belonging to a group working towards a common goal. It acts as a catalyst in motivating them to strive for their recovery and well-being.

Some examples are below:

- Appropriate fiscal support and advice can help people struggling with financial difficulties.
- Relationship advice and counselling services are beneficial in harvesting and empowering the family support in the community.
- Workplace based interventions offered by employers have evidenced not only better work-efficiency, but also improved the quality of life of its workforce.

### **III. Focussed therapies**

Patients with well-adjusted personalities who experience extreme form of stress or develop a diagnosable psychiatric illness secondary to stress benefit from therapies that analyse and change the way they appraise the situation and/or the way they respond to it. These therapies are aimed at bringing about change in the person's maladaptive way of responding or reacting to stressors. Focussed therapies are based on specific theories such as Cognitive theory, Behavioural theory, Interpersonal theory, Psychodynamic theories, Mindfulness theory Transactional theory or a combination of theories. The primary aim of focused therapies is to restore individual's functioning to previous level. However, in some therapy may result in, personality change, personal growth and enhanced psychological functioning through new learning.

Some examples of focussed therapies are given below:

#### ***Cognitive Behavioural Therapy (CBT)***

This is the most common form of talking therapies in recent times with evidence for effectiveness. Some advocate CBT as the Gold standard psychotherapy for stress management (David, 2018).

In a broad sense the therapies aim to reappraise the situation that brought about the stress and correct the maladaptive thought process. Any situation is primarily evaluated by people in terms of its nature and relevance to themselves, and as such is called the Primary Appraisal. They then examine and evaluate the next steps to follow which is called the Secondary Appraisal. (Lazarus & Folkman 1984)

The Primary appraisal can either be irrelevant, benign-positive or stressful. If perceived as 'irrelevant', the issue is of no value to the subject and there is nothing

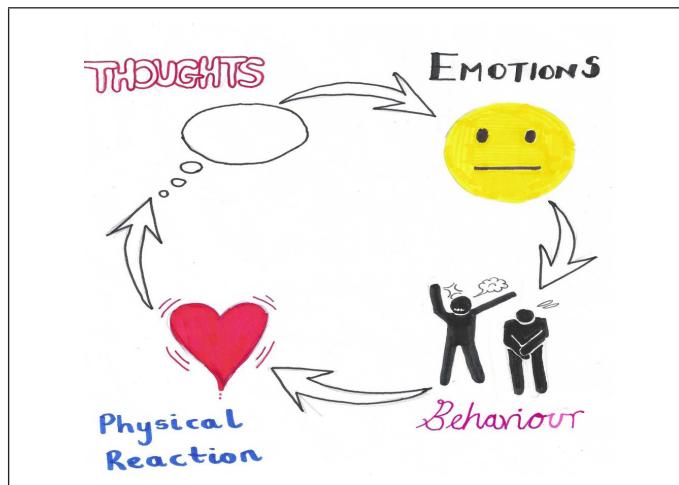
to be lost or gained. ‘Benign-positive’ appraisals occur when the result of a process is perceived as positive or beneficial to one’s well-being. Those appraised as ‘Stress’ include some form of harm, threat or challenge. The Secondary appraisal is a complex process involves evaluation of available coping options, select the best that suits to the situation and analyse the consequences of using it in that specific scenario.

The interactions between primary and secondary appraisals determine any individual’s emotional reaction to the stressor. Additionally, their commitments (values and goals) and beliefs influence their reactions. The way a person appraises a situation is evident in their thoughts and actions. It is important to mention here the concept called Cognitive Reappraisal which involves construing a potentially emotion-eliciting situation in a way that changes its emotional impact.

CBT targets the problem at appraisal level and assumes that perception involves both inspective and introspective processes. During the therapy, the patient is supported to understand how thought patterns, feelings, physical reactions and behaviours interact with each other to maintain and/or perpetuate problems.

Cognitive techniques help the patient identify and test negative or maladaptive cognitive patterns (automatic thoughts, dysfunctional beliefs and attitudes) and correct the dysfunctional constructs in order to practise more helpful behaviours.

Figure 3: Cognitive Behaviour Therapy Cycle



The behavioural principles are used either alone, most often together with cognitive theories in CBT. The commonly employed behavioural techniques are:

- Relaxation training: like breathing exercises and progressive muscle relaxation are taught and practised regularly during sessions.
- Exposure: is used to unlearn and reduce avoidance behaviour or suppression which is an unhelpful defence mechanism to handle stress. The patient is then encouraged to use and practise positive coping methods and relaxation techniques.
- Behavioural activation: where the client is supported to identify specific goals which he/she was hitherto avoiding and is then encouraged to work towards achieving these.
- Social skills training: like basic communication skills, assertiveness training and anger management

### ***Stress Inoculation Therapy (SIT)***

SIT is a type of CBT developed by Donald Meichenbaum in 1977 (Meichenbaum & Deffenbacher 1988). SIT incorporates the concept of ‘stress inoculation’; the term ‘inoculation’ being used to show how it is akin to ‘vaccination’ in the prevention of stress. In SIT, patients are first educated about stressful situations and the general nature of stress. They then learn about their own vulnerabilities for negative outcomes when confronted with stress and the steps they can take to avoid those negative outcomes.

Skills tailored to the needs of the individual are taught. These include a range of methods such as emotional regulation, relaxation techniques, problem-solving skills, self-soothing, effective communication skills, mindfulness training, and distraction techniques. The therapy can be delivered in individuals, couple or group settings; and consists of 8-15 weekly or biweekly sessions (max 40 sessions) of 20-60 minutes each over 3-12 months.

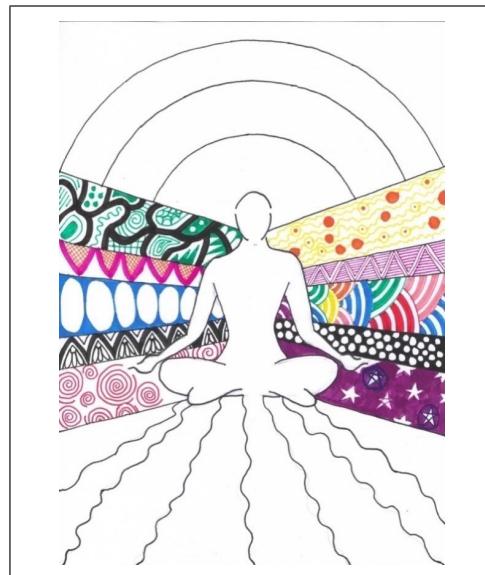
### ***Mindfulness-Based therapies:***

Mindfulness based treatment approaches have been successfully used in managing stress, especially in patients with personality disorders. Some of the techniques include Mindfulness-based stress reduction (MBSR), Mindfulness-based cognitive therapy (MBCT), Dialectical Behaviour Therapy (DBT) and Acceptance and Commitment therapy (ACT). (Baer, 2006)

***Mindfulness-Based Stress Reduction (MBSR)***

MBSR was introduced by Jon Kabat-Zinn in the 1980s (Kabat-Zinn, 2013). It is based on Buddhist teachings on mindfulness which aims to reduce how the body gets aroused in a situation. It involves intensive training in mindfulness, meditation and yoga.

**Figure 4: Mindfulness-based Treatments**



MBSR is an eight-week program with weekly sessions lasting 2-3 hours and a day-long intensive mindfulness session during the sixth week.

These were mainly developed for patients with poor coping and habitually maladaptive behaviours secondary to their personality traits. Like in all psychological treatments, therapeutic relationship lies at the heart of these therapies.

Mindfulness-based cognitive therapy (MBCT) is another therapy based on Buddhist teachings and use of cognitive and behavioural theories in addition.

***Mindfulness-Based Stress Reduction for Teens (MBSR-T)***

MBSR-T combines the concepts of the MBSR program for adults and the mindfulness-based cognitive therapy. The therapy is based on the developmental theory and the program is designed taking into consideration the attentional abilities and the unique cultural environment and demands of young people aged

13-18 years. It has also been utilised in schools, children's hospitals and inpatient psychiatric settings. The therapy can be delivered as a stand-alone modality or as an adjunct to other therapies.

MBSR-T aims to empower young people with skills and tools to help them function more adaptively and improve their quality of life. It is delivered as eight weekly sessions lasting 90 minutes each. Some of the skills taught in this program are mindfulness, breathing exercise, relaxation strategies, communication and problem-solving skills.

#### ***Acceptance and Commitment Therapy (ACT)***

ACT takes a pragmatic approach to help the patient develop 'psychological flexibility' which essentially means accepting themselves and the situation WITHOUT the need to use defences AND responding to the situation in a practical and practicable way (Ackerman, 2020).

It examines the consequence of a behavioural response to stress on how it 'functions' or 'works' for the patient in the specific context or situation. Most importantly, the therapy swerves away from judging whether the response was wrong, bad or abnormal. The focus of this therapy is thus on the function that the behaviour is achieving; and then aims at changing this and not on 'targeting' or 'fixing' the behaviour itself.

#### **IV. Long-term Therapies:**

Long-term psychotherapies benefit people who suffer from personality disorders. Patients with personality disorders often suffer from chronic stress, mainly as an upshot of long-established and deep-rooted distorted or negative cognitions and habitual use of maladaptive coping strategies to manage life. This in turn impacts on the quality of relationships, life choices, employment and education, physical health, opportunities to achieve life goals and general self-worth. Poor self-image and self-esteem thus perpetuate a vicious cycle of hopelessness and dissatisfaction leading to overall poor quality of life and high Disability-adjusted life years (DALYs).

The aim of the therapy is to modify the habitual pattern of coping by providing insight into enduring maladaptive personality characteristics. These therapies are designed to be delivered over several weeks to months, taking into consideration

the enduring nature of personality disorders, the complexity and longstanding nature of the problems. Each session is of a longer duration than other therapies with homework given at the end of each. Refresher sessions can also sometimes be provided in order to reinforce and practise skills learned during therapy.

The examples of long-term therapies include several forms of psychoanalysis such as Freudian psychoanalysis, Kleinian psychoanalysis, Transactional analysis, and Existential analysis. Therapeutic community is another long-term intervention aimed at personality change by environmental manipulation. However, such therapies are not in current use in the same form because they are intensive, prolonged and expensive and have undergone modifications to current circumstances. It is beyond the scope of this book to delve into such therapies. Hence, we have provided a brief account of Dialectical Behaviour Therapy (DBT) which is currently used for personality disorder and Therapeutic Community for its historical importance.

### **Dialectical Behaviour Therapy:**

High emotion efficacy is a strong protective factor against stress. In other words, people who are able to experience and respond to a full range of emotions in a flexible, adaptive and consistent manner are also able to utilise and benefit from positive emotional coping (Matthew, 2016).

According to Matthew McKay (Matthew, 2016), some biosocial factors make people more vulnerable to emotional dysregulation:

- Biological predisposition to high levels of emotional reactivity
- Significant levels of emotion avoidance or efforts to avoid experiencing perceived or actual uncomfortable emotions and cognitions
- High levels of distress intolerance
- Poor emotion-regulation skills
- Consistent and significant socially invalidating environments

Emotion efficacy is especially poor in people with personality disorders who experience difficulties related to both over and under control of emotions, impulse control, interpersonal relationships and self-image (Marsha, 2014). These can

be collectively considered under the umbrella of emotional dysregulation and addressed in Dialectical Behaviour Therapy or DBT.

DBT was introduced by Marsha M. Linehan in 1994 and combines aspects of CBT with the practice of Mindfulness. It is based on the dialectical and biosocial theory of psychological disorder that emphasizes the role of difficulties in emotional regulation and behaviour. It has proved most beneficial in whom stress is due to maladaptive coping strategies which are characteristic of their personality disorder (most commonly borderline personality disorder).

The ‘Dialectical’ part of DBT deals with how two things can seem opposite and still be true. The Biosocial theory explains the biological and social aspects of emotion regulation and the impact of the interactions between the two.

The following skills are taught in DBT:

- Mindfulness skills
- Interpersonal effectiveness skills
- Emotion regulation skills
- Distress Tolerance Skills (includes Crisis survival skills and Reality acceptance skills)

The therapy usually consists of weekly individual and group sessions. In addition, patients are offered telephone contacts in between sessions to reinforce use of skills learnt during sessions in everyday life. The length of therapy varies from 6 months to three years depending on the severity of the problems and availability of resources. In recent times it is modified to shorten the duration to six months to one year while retaining the core principles of the therapy (McMain et al., 2018).

### ***Therapeutic Communities***

Therapeutic communities were specifically introduced for the treatment of personality disorders and the stress arising from it. These are therapeutic settings designed for patients to live, work and play together in a group setting while learning and practising new behaviours. There is opportunity to understand themselves through the reactions of others while also respecting their views and ideas. The concept was founded by Maxwell Jones and is based on four major principles of the Henderson hospital model. These are:

- Communality (patients live and support each other to help bring about change)
- Democratisation (shared decision making and joint running of the unit)
- Reality confrontation (reality of situations are accepted and confronted honestly and openly by all members)
- Permissiveness (patients tolerate behaviours and unpredictability that they hitherto did not)

## SUMMARY OF VARIOUS THERAPIES USED FOR MANAGEMENT OF STRESS

Table 1: Psychological therapies for Stress

Intervention/ Therapy	Key Concepts/theory	Uses
Cognitive Behavioural Therapy	Cognitive theory (Primary Appraisal, Secondary Appraisal and Cognitive Reappraisal)  Cognitive restructuring  Guided discovery  Behavioural Theory	Stress and anxiety  Adjustment difficulties and disorders  Loss and life changes  Bereavement  Chronic physical illnesses and Cancer
Interpersonal Therapy	Loss or Grief  Interpersonal disputes  Role transition  Interpersonal deficits	Stress and anxiety  Interpersonal role changes  Interpersonal conflict  Relationship difficulties  Bereavement
Client-centred Therapy	Empathy  Non-directive  Unconditional positive regard	Chronic stress  Work-related difficulties  Role confusion  Self-esteem and confidence related problems
Behaviour Therapy	Learning theory	See above CBT
Cognitive therapy	Cognitive theory or Cognitive model	See above CBT
Stress Inoculation Therapy	Cognitive and Behavioural theory 'Stress inoculation'	Stress

Intervention/ Therapy	Key Concepts/theory	Uses
Acceptance and Commitment Therapy	Cognitive and Behaviour theories 'Psychological flexibility'	Stress and anxiety Major life events and changes Chronic physical illnesses
Mindfulness-based stress reduction	Buddhist teachings of Mindfulness Coping methods Cognitive and Behavioural theories	Stress and anxiety Adjustment difficulties
Mindfulness-based Stress Reduction for Teens	Buddhist teachings of Mindfulness Age specific coping methods and skills Cognitive and Behavioural theories	Stress, anxiety and adjustment difficulties in teens
Psychodynamic Psychotherapy	Psychoanalysis Psychodynamic theory	Stress with Personality disorder Relationship problems Attachment disorders
Cognitive Analytic Therapy	Procedural sequence model Role repertoires	Chronic stress and anxiety Personality disorders
Dialectical Behaviour Therapy	Cognitive and Behavioural theories Distress Tolerance Interpersonal effectiveness Core mindfulness Emotional regulation	Chronic stress and anxiety Personality disorders (especially borderline personality disorders)
Therapeutic Communities	Henderson hospital model (Community, Democratisation, Reality confrontation, Permissiveness)	Chronic stress in Personality disorders

## PREVENTION OF STRESS

Although the focus of the chapter is psychological management of stress, it would be incomplete without an account on preventative aspect of stress. Therefore, a brief summary of the broad range of interventions advocated for prevention of stress are provided below.

### **General measures**

Pre-emptive management of stress involves adapting healthy lifestyle such as healthy and balanced diet and regular exercise, reducing caffeine and sugar intake, avoiding cigarettes and non-prescription drugs, cutting down alcohol, good sleep hygiene, and meditation and relaxation exercises.

### **Life skills training programmes:**

These programmes attempt to provide tools to individuals to easily and effectively handle everyday problems. Clients are taught critical-thinking, communication and team-working skills, decision making and problem-solving skills. These have been successful in both adults and young people and can be delivered in both individuals and group settings.

### **Stress Management programmes:**

CSSP (Comprehensive Stress Prevention Programme) can be arranged at workplaces or organisations for both employees and employers. These are tailored to the workforce and the stressors specific to the job profile. The programmes aim to encourage better communication, negotiation and participation in order to effectively reduce work-place stress and improve productivity.

### **Relaxation techniques**

These include Progressive muscle relaxation training and Deep breathing exercises are commonly used and have shown promising outcomes.

### **Biofeedback:**

This is a process which uses sensors to measure heart rate, respiratory rate and muscle tension to help the individual understand his or her body's response to stress and the impact of the environment on the same. It thus helps them become more aware of these changes when faced with stressful events in the future and thereafter, manage the situation better.

## **STRESS MANAGEMENT FOR HEALTHCARE PROFESSIONALS**

Stress among health professionals is common and perhaps deserves to be addressed as a separate chapter. However, we have included the following section to provide a brief overview.

Healthcare professionals are programmed to care for their clients while tending to ignore their own physical and mental well-being. Besides, health professionals frequently undermine work-related stress and sometimes actively deny the existence of the same.

Benefits of psychological interventions for healthcare professionals are multi-faceted:

***Self-care and coping:*** Health professionals are high at risk of burn-out with busy schedules, administrative paperwork and vicarious trauma (compassion fatigue) posed by their work. Some characteristics about their personalities like workaholic mentalities, lack of clear boundaries, inability to say no and poor time-management skills also make them more vulnerable to stress. Inevitably, such stress impacts on their performance and thus the quality of care provided to the patients. This can then lead to anxiety, hopelessness and depression; and indirectly to relationship difficulties and poor quality of life. In these cases, prevention and early treatment of stress makes a huge difference to the professional and their clientele.

***Becoming a ‘mindful’ clinician:*** Mindfulness practices help develop personal qualities and professional skills like empathy, attention and emotional regulation that are beneficial to clinical practice. It also helps the clinician provide empathic care, while maintaining therapeutic detachment from the patient’s personal suffering.

***Providing mindfulness-informed therapy to clients:*** This essentially means integrating the aspect of mindfulness into all other treatments. The clinician can help patients accept the reality of constant change and support them to understand and accept that their body, feelings, thoughts and perceptions can constantly change. These are also found to enhance therapeutic relationship, engagement and overall outcomes.

## **MEASUREMENT OF EFFECTIVENESS OF THERAPY**

Finally, it is beneficial to quantify the severity of stress before initiation, midway and at the completion of therapy; preferably using structured instruments. This enables the therapist to follow the progress of therapy, identify issues that need addressing and shape upcoming sessions. For patients, it serves as a visual feedback to motivate them, encourage future engagement and instil confidence and hope. It

is essential to select appropriate tools to measure and record meaningfully. The tools need to be easy to administer, generalizable and work for a variety of therapy modalities. Some of these are given below:

1. Clinical Outcome in Routine Evaluation – Outcome Measures (CORE-OM) score: This is a patient-rated measure of well-being and functioning. It is easy to administer and works well for many different types of psychological therapies (Evans, 2002).
2. Inventory of Interpersonal Problems (IIP): a clinician-rated scale of interpersonal functioning (Horowitz, 1988).
3. Work and Social Adjustment Scale (WSAS): is a simple-to-use patient-rated measure of impaired functioning and social or work adjustment. It is also a reliable and sensitive tool to measure, offering the potential for readily interpretable comparisons across studies and disorders (Mundt, 2002).

## **CONCLUSIONS**

There is ample evidence that continuous, intense or chronic stress is detrimental to human well-being and can have both short-term and long-lasting consequences on our physical and mental health. This has been acknowledged and addressed as much in ancient scripture as in today's modern psychotherapy. Current practices favour a combination of medications and psychological therapies for optimal management of stress.

There are a range of psychotherapy modalities to choose from and tailor to the client's needs; including but not limited to lifestyle changes, self-help and structured psychological therapies. With training and appropriate supervision, many of the therapies can be delivered by health professionals with a variety of expertise and backgrounds.

Effective stress management has proven to improve not only mental health, but also physical and intellectual health and overall quality of life. These have also shown indirect benefits of reduced DALYs, enhanced employee productivity and reduced absenceism.

It is imperative to introduce the subject of stress and its management to children as early as pre-teens and equip them with necessary coping skills. Doing

this enables them to not only recognise stress in themselves and ask for help when needed; but also, to recognise it in peers, offer supportive help and signpost them in the appropriate direction.

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## **TRADITIONAL METHODS OF STRESS MANAGEMENT**

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### **OUTLINE**

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| 3. MIND-BODY THERAPIES                 | 4. ENERGY-BASED THERAPIES       |
| 5. BODY-BASED/ MANIPULATIVE THERAPIES  | 6. WHOLE MEDICAL SYSTEMS        |
| 7. OTHER TRADITIONAL HEALING PRACTICES | 8. CONCLUSIONS                  |

## **INTRODUCTION**

Life exists through the maintenance of a complex dynamic equilibrium, termed **homeostasis**, which is constantly challenged by internal or external adverse forces, termed **stressors**, which can be emotional or physical in nature. Thus, stress is defined as a state of threatened (or perceived by the individual as threatened) homeostasis, and the equilibrium is re-established by a complex repertoire of behavioural and physiologic adaptive responses of the organism.

The “**Stress Response System**” located in the central and peripheral nervous system is generically activated whenever a threshold of any stressor is exceeded, and plays a major coordinating role in the re-establishment of homeostasis by eliciting a complex behavioural and physical adaptive response. This response is defined as the **stress syndrome** and represents the unfolding of a relatively stereotypic,

innate program of the organism that has evolved to coordinate homeostasis and protect the individual during stress. **Neuro-endocrine hormones** have a crucial role in coordinating basic as well as threatened homeostasis; also, they intervene in pathogenesis of dyshomeostatic situations of disease (Varvogli & Darviri 2011).

Methods of preventing and managing stress have been avidly sought by people worldwide. Most of such methods or practices that have been used to prevent stress or deal with disorders arising out of stress are derived from local traditions and cultural contexts and can be considered under the rubric of **Traditional Medicine (TM)**. The World Health Organization (WHO) estimates that between 65 and 80 percent of the world's health care services are currently classified as traditional medicine, and in many countries, constitute the major form of treatment.

According to the WHO, traditional medicine is “**the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses**” (WHO, 2003). It is a comprehensive term used to refer to TM systems such as traditional Chinese medicine, Indian Ayurveda and Arabic Unani medicine, and various forms of indigenous medicine. In countries where the dominant health care system is based on allopathic medicine, or where TM has not been incorporated into the national health care system, TM is often termed “**complementary**”, “**alternative**” or “**non-conventional**” medicine. In complementary medicine, some approaches can be, and are used, in conjunction with conventional biomedical treatment. Other terms to describe these therapeutic approaches are **integrative medicine** and **holistic medicine** (Sadock et al. 2007)

TM continues to be very widely used in most developing countries, particularly in the rural areas because of better accessibility and traditional belief systems embedded in the culture. TM accounts for a very significant proportion (around 40%) of all health care delivered in China, with strong support by the government. **Complementary and Alternative Medicine (CAM)** is also becoming more popular in most developed countries. According to data from the WHO, a significant proportion of the population in developed countries have also used CAM at least once (48% in Australia, 70% in Canada, 42% in USA, 38% in Belgium and 75% in France) (WHO 2002). In this background, the WHO launched its first ever **comprehensive traditional medicine strategy** in 2002. The strategy is designed

to assist countries to promote research and development, while improving quality, availability, and affordability of TM/CAM

The **United States National Centre for Complementary and Alternative Medicine (NCCAM)** has grouped CAM into **five broad categories**: Biologically based therapies, mind-body therapies, energy-based therapies, body-based manipulative therapies and whole medical systems (Wieland et al., 2011).

**Box 1. Classification of CAM into 5 broad categories by US National Institute of Health's NCCAM**

<b>Biologically based therapies</b>	Natural Product Based Therapies, which use substances found in nature to promote health. E.g. dietary supplements and herbal remedies
<b>Mind-body therapies</b>	Use techniques that enhance the capacity of the mind to affect bodily function and symptoms. E.g. Yoga, Qigong and meditation.
<b>Energy-based therapies</b>	Involve the use of energy fields, either electromagnetic fields or the manipulation of energy fields that purportedly surround and penetrate the human body. E.g. qi gong, therapeutic touch, reiki magnet therapy.
<b>Body-based manipulative therapies</b>	Therapies based on manipulation and/or movement of parts of the body. E.g. Chiropractic and osteopathic manipulation and massage.
<b>Whole medical systems</b>	Complete systems of theory and practice outside the conventional allopathic model. E.g. Traditional Chinese medicine, Ayurveda, Homeopathy, Naturopathy

## BIOLOGICALLY BASED THERAPIES

This section mainly focuses on the use of herbs and supplements in traditional medicine. **Herbal medicine** uses plant products to maintain health and treat illness. It is the **oldest known system of medicine**, its historical origins attributed to **China** in approximately 4000 BC, but, certainly, plants have been used medicinally worldwide throughout prehistory. A **Greco-Roman medical** text by Dioscorides,

*De Materia Medica*, in the first century, describes the use of more than 500 plants to treat disease, beginning a tradition followed in European medicine to this day.

In this context, it is important to introduce the term “**adaptogen**”. It was originally used by N. V. Lazarev (1947) to refer to a substance which was claimed to increase “non-specific” resistance of an organism to adverse influences and stress. Today adaptogens are conceptualized as a “new class of metabolic regulators (of a natural origin) which increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors” (Panossian et al. 1999). The concept of adaptogens as “medicine for the healthy” or in helping the body cope with stress is a great deal similar to many remedies common in Chinese herbology. **Ayurveda**, the traditional medical system of India, has a similar concept of **rasayana**. Various substances are classified in this tradition as rasayanas, meaning they are believed to promote physical and mental health, improve defense mechanisms of the body and enhance longevity (Bhattacharya et al. 2000)(Rege et al. 1999). Herbalists refer to adaptogens as rejuvenating herbs, qi tonics, rasayanas, or restoratives

Although adaptogenic plants that have been traditionally employed in many countries for centuries, they require clinical evaluation of their efficacy and safety before they can be recommended widely. Though many of the herbal substances described below are claimed to be adaptogens, Rhodiola rosea, Eleutherococcus senticosus, and Schisandra chinensis are the most extensively studied and listed adaptogens (Panossian, 2013). Some of the herbal medicines and adaptogens are described below.

St. John’s Wort: The flowering tops of Hypericum perforatum or St. John’s wort (SJW) have been used through millennia for a range of systemic nervous conditions, including depressed mood.

Numerous trials have proven its efficacy in **major depression**. SJW contains a range of constituents, of which the active component is **hypericin**. It works by **non-selective inhibition** of neuronal uptake of serotonin, dopamine, noradrenaline, and weak inhibition of monoamine oxidase A & B enzymes. It also causes favourable **epigenetic changes**, up-regulating genes involved with inflammatory changes and oxidative stress, and its use has been associated with significantly higher levels of serum BDNF in depressed patients compared to other medications (Sarris, 2013).

Current evidence supports the use of high-grade, standardized SJW extracts for the treatment of **mild-to-moderate depression and somatisation disorder**, with tentative support in **seasonal affective disorder**.

Figure 1: St. John's wort (*Hypericum perforatum*)



Courtesy: Donald Cameron. Copyright @ 2014, Donald Cameron, from <https://gobotany.newenglandwild.org/species/hypericum/ellipticum/>

**Ginkgo biloba:** The ancient ginkgo tree (*Ginkgo biloba*) is one of the oldest tree species on earth. Its fossil records date back to a staggering 200 million years! Because of its great age in the spectrum of geologic time, ginkgo epitomizes persistence-fighting the odds and surviving. As a medicinal herb, ginkgo is best known for its improvement of **short-term memory**, but it has also been described to be effective in treating **allergies, depression, poor circulation** and many more conditions.

It is one of the most prescribed herbal preparations in Germany and an over-the-counter herbal preparation in the United States. It has many potentially bioactive compounds, however, the most standardized extract is **EGB 761** (Diamond & Bailey 2013). Indications of its use are in generally one of the 3 categories: **cerebro-vascular, peripheral vascular, or tissue damage**. Its **putative neuro-protective and cognitive-enhancing properties** have provided support for its use in treating

neurological, psychiatric, functional, and physiologic symptoms including problems with memory, information processing, attention and concentration, psychomotor function, mood, fatigue, and activities of daily living (Ponto & Schultz 2003). It has anti-oxidant properties, enhances cerebral blood flow via antagonism of platelet activating factor, and appears to enhance glucose metabolism(Meeks & Jeste 2009). Common indications include **Alzheimer's dementia, normal aging-related cognitive deficits, traumatic brain injury, stroke, multi-infarct dementia, cerebral atherosclerosis, cerebral insufficiency, cerebral oedema, inflammation, intermittent claudication**, with some work suggesting benefits in **multiple sclerosis** (Diamond & Bailey 2013). There is also evidence that G. biloba can serve as an augmenting agent with **conventional antidepressants** (Kiresuk & Trachtenberg 2005).

**Saffron:** Saffron, the world's most expensive spice, is derived from the flower of Crocus sativus. Originating in Crete, its stigma and petal have been used for thousands of years and is mentioned in a 7th century BC Assyrian botanic text. It has been found efficacious and tolerable in management of **mild to moderate depression**, owing to its monoamine uptake inhibition, improved BDNF signaling, and NMDA antagonism. The latter effect, combined with acetylcholinesterase inhibition, is responsible for improvement in cognitive function in patients with **Alzheimer Disease**(Modabbernia & Akhondzadeh 2013). It also has neuro-protective and anti-inflammatory properties. In patients with **Premenstrual syndrome**, it has been shown to reduce anxiety along with reduced cortisol levels and improved estrogen levels. It also improves sexual functioning in patients with **erectile dysfunction**.

**Passion flower:** PPassionflower (Passiflora incarnata) (Krishna kamala in Sanskrit) is a woody, hairy, climbing vine that was used traditionally in the Americas and later in Europe as a calming herb for anxiety, insomnia, seizures, and hysteria. It holds a lot of religious significance in the Christian faith as it resembles the crown of thorns said to have been worn by Jesus Christ during the crucifixion; and also in the Hindu faith, symbolising the holy trinity (Brahma-Vishnu-Maheshwara). It works by increasing levels of gamma aminobutyric acid (GABA), which is an inhibitory neurotransmitter in the brain. Studies of the effects of passionflower in the treatment of **sleep and anxiety disorders** have been promising(Modabbernia & Akhondzadeh., 2013). It has also been successfully used as a calming agent before

surgery and as an adjunct to clonidine in the **treatment of opioid withdrawal**. It has been used as a herbal tea or tincture. It is listed as a safe **herbal sedative** by the US Food and Drug Administration.

**Valerian:** Valerian extract is obtained from the dried rhizome and roots of the perennial herb, *Valeriana officinalis*. Known to Hippocrates and Galen, it has traditionally been used for **insomnia, anxiety, seizures, and migraine**. Studies have shown modest benefit in **sleep and anxiety disorders** (Modabbernia & Akhondzadeh., 2013).

**Ginseng:** Ginseng can refer to a variety of species within the genus *Panax*, which in Latin means “all-healing”. This reflects its long-standing use in traditional Asian cultures for a variety of reasons. **Korean or Asian ginseng** (*Panax ginseng*) has been the most commonly studied among others and has been touted to benefit individuals with problems such as **fatigue, sexual dysfunction and diabetes mellitus**. **It improves exercise performance** via improvements in muscular strength, maximal oxygen uptake, work capacity, fuel homeostasis, serum lactate, heart rate, visual and auditory reaction times, alertness, and psychomotor skills which have been repeatedly documented(Kiresuk & Trachtenberg 2005). **Side effects** include over-stimulation, anxiety, insomnia, tachycardia, gastrointestinal disturbance, headache, and reduced platelet aggregation (Gerbarg & Brown., 2013).

**American ginseng** (*Panax quinquefolius*) is less activating than Asian ginseng. The use of ginseng in the treatment of sexual dysfunction is common in Asia. The effects of ginseng on the corpus cavernosum appear to be mediated by the release or the modification of release, or both, of nitric oxide from endothelial cells and perivascular nerves. American ginseng has been shown to affect the activity of hypothalamic catecholamines involved in the facilitation of copulatory behavior and hormone secretion (Kiresuk & Trachtenberg., 2005). **Siberian ginseng** (*Eleutherococcus senticosus*) is believed to help **fatigue and stress**, to improve endurance, and to have immuno-stimulatory properties. It has been shown to improve sleep, well-being, appetite, stamina, cognitive function, and mood in patients with neurosis, without significant side effects. In patients with **idiopathic chronic fatigue** it has shown improvement in vitality. It has been studied in **bipolar depression** as an adjunct to mood stabilizers, showing favourable preliminary evidence (Panossian, 2013).

**Huperazine A:** Huperazine A (HupA) is a plant-based alkaloid derived from the club moss *Huperzia serrata*, which has been used for centuries in China as folk medicine for **fever, inflammation, analgesia, and even in schizophrenia and myasthenia gravis**. It is sold in the US as a dietary supplement. It is a strong, selective acetyl cholinesterase inhibitor with neuroprotective properties, including protection against free radicals, amyloid- $\beta$  protein formation, glutamate, and ischemia. It protects mitochondria, reduces oxidative stress, and up-regulates nerve growth factor. It improves **learning and memory** and has shown positive outcomes in studies on mild to moderate **Alzheimer disease, vascular dementia, traumatic brain injury, age-related memory decline, and schizophrenia**(Gerbarg & Brown., 2013).

**Snowdrop** (Galantamine): In folk medicine of Russia and Europe, extract of snowdrop (*Galanthus nivalis*) was used to prevent age-related memory decline. It is an allosteric modulator of nicotinic receptor and weak inhibitor of acetyl cholinesterase. **Galantamine** is a synthetic copy of 1 component of snowdrop, and is FDA approved for the treatment of **Alzheimer disease**(Gerbarg & Brown., 2013).

**Kava:** Kava extract is obtained from the Pacific Island plant, *Piper methysticum*. It has been used in traditional Island ceremonies and has mood-altering characteristics. It contains **kava lactones and  $\alpha$ -pyrones** which increase GABA transmission, blocking of lipid membrane sodium and calcium channels, dopamine antagonism, and modulate of serotonin and glutamate levels. It inhibits P450 enzymes, CYP 3A4 and CYP2D6 and there have been case reports of hepatotoxicity. Abuse has also been reported as it produces a natural high, along with mental and physical relaxant effects. Evidence supports the use of kava for **anxiety** but safety issues need to be addressed (Gerbarg & Brown., 2013).

**Green tea:** Tea leaves are obtained from the plant *Camellia sinensis*, and different varieties of tea are produced according to the changes in the fermentation process. Green tea has been used for centuries for calming and medicinal effects. Green tea contains a **polyphenol, epigallocatechin-3-gallate (ECGC)**, with anti-inflammatory properties. **Theanine** is an amino acid found in green tea responsible for the mild relaxing effect, possibly by inhibition of cortical excitation. It also exerts antioxidant and anti-proliferative effects. Green tea extract is also high in catechins, which have reported efficacy in **reducing obesity** (Meeks & Jeste

2009). The caffeine in green tea may increase blood pressure and worsen anxiety; therefore, decaffeinated green tea has been used for mild to moderate anxiety in clinical settings.

**Chamomile:** German chamomile (*Matricaria recutita*) has a mild hypnotic effect and has been used in a variety of **GI problems, mouth and skin irritation, paediatric colic and teething, and mild insomnia and anxiety**. It contains **apigenin**, which has high affinity for benzodiazepine GABA receptors, modulates monoamine neurotransmission and has neuro-endocrine activity. Chamomile extract has been studied and found efficacious in **mild to moderate anxiety**(Gerbarg & Brown., 2013).

**Arctic root:** *Rhodiola rosea* was described by Dioscorides in *De Materia Medica*. It grows in cold regions of the world, including mountains of the Arctic. The roots contain six groups of bioactive compounds, with SHR-5 its standardized extract being used clinically. It has been shown to be efficacious in many stress-related conditions including **fatigue, cognitive dysfunction, memory problems, depression, sexual dysfunction, weakness, infection, and in cancer**. When given alone or in combination with other adaptogens, it can enhance physical and intellectual performance, attention and memory. It has shown a pronounced therapeutic effect on **neuroleptic-induced parkinsonian symptoms** and **fatigue** in subjects with **schizophrenia** (Panossian, 2013).

**Schizandra** (*Schisandra chinensis*): Chinese folklore says that *Schisandra* can “calm the heart and quiet the spirit”, and it has a long history in Traditional Chinese Medicine. Extracts of its fruits and seeds have been used to reduce symptoms of stress such as fatigue and weakness, to enhance physical performance, and to promote endurance. It is useful as an adjunctive treatment for **sluggish depression, chronic fatigue, and fibromyalgia**. Trials in patients with mental disorders have shown that it eliminated catatonic stupor, promoted **remission of hallucinations in patients with schizophrenia**, and hastened the **resolution of alcoholic delirium** (Panossian, 2013).

**Aromatherapy:** Aromatherapy is the medical use of pure essential oils that are extracted from plants. The therapeutic, spiritual and cosmetic use of aromatic oils has at least a 5000-year history. A pure essential oil is the “soul” of the plant where the vital energy of the plant is stored. Different oils are believed to have different

therapeutic properties because of their varying chemical compositions. The essence is produced by special cells within the plants and contains ‘**phytohormones**’ that, like human hormones, transmit cellular information throughout the body in response to stress and environmental conditions. The vital essences of plants are converted into pure essential oils and aromatic hydrosols by the mechanical process of steam distillation. ‘**Phytotherapy**’ incorporates the use of essential oils by ingestion (tinctures, liniments, infusions) and is often combined with, or used interchangeably with, aromatherapy. Plant oils are also said to have analgesic, psychological, and antimicrobial effects. For instance, oil of cloves is a commonly used dental analgesic.

Ayurveda employs aromatic massage using infused oils made from indigenous herbs and woods. Aromatherapy is said to relieve stress and anxiety and to alleviate **GI and musculoskeletal disorders** among others. The Greeks and Romans used aromatics in the treatment of mental illness. In psychiatry, **olfactory stimulation** has been used to elicit feeling tones, memories, and emotions during psychotherapy. Studies have examined how aromatherapy may work to relieve **anxiety** in medical and work settings (Sgoutas-Emch et al. 2001).

## MIND-BODY THERAPIES

The NIH has defined mind-body therapies as “interventions that use a variety of techniques designed to facilitate the mind’s capacity to affect bodily functions and symptoms.” The mind-body therapies discussed in this section are Yoga, *Qigong* and meditation.

**Yoga:** Yoga (“yoking” or “union” in Sanskrit) is an ancient way of life, which was intended to help individuals consciously evolve spiritually. Early evidence of Yoga practice dates back 5,000 years ago in India, and it has been practiced as a spiritual and health system ever since. Yoga has been defined as the process of gaining mastery over fluctuations in the mental state (*Yogah chitta vritti nirodhah*). The ancient Indian text, the Bhagavad Gita, describes Yoga as “**skill in action**”.

The first compilation of Yoga in a scientific manner was attempted by sage Patanjali around 900 BC who formulated the ‘*Ashtanga*’ or eight-limbed model (*yama* or a moral code of conduct, *niyama* or observation of rules, *asanas* or physical postures, *pranayama* or breath regulation, *pratyahara* or sense-withdrawal, *dharana* or concentration, *dhyana* or meditation, and *Samadhi* or absorption into

universal consciousness). Over the last century, numerous Yoga schools or ways of teaching have emerged, such as **Iyengar Yoga, Bikram Yoga, Kriya Yoga, and Hatha yoga** which includes mainly asanas as practice. The West grew familiar mainly with the latter practice. These Yoga styles vary in their emphasis on breathing, movement and meditation.

**Figure 2:** A yoga practitioner illustrating various yogic postures (asanas).  
Top left: Ustrasana; Bottom left: Rajakapotasana; Right: Sarvangasana



Courtesy: Shwetha Yogini, NIMHANS Integrated Centre for Yoga, 2013  
(with permission).

**Breath regulation** is given much importance in Yoga. Pranayamas (Sanskrit: *prana* = life energy or vital force; *ayama* = to prolong) are voluntarily regulated yoga breathing techniques. This includes several practices such as high frequency breathing (*Kapalbhati*), single and alternate nostril breathing, breathing with a period of breath holding (*Kumbhaka*), bellows type breathing (*Bhastrika*), *Ujjayi* pranayama in which there is breathing with partial closure of glottis, and many more.

Research demonstrates that Yoga practice can modulate **autonomic nervous system function**, stress responses, cardiac vagal tone, heart rate variability,

vigilance, attention, chemoreflex and baroreflex sensitivity, **central nervous system excitation**, and **neuroendocrine functions**(Telles & Singh 2013). Studies have also shown an **improvement in telomerase activity**, suggesting benefit in stress-induced cellular ageing. Yoga-based practices are very popular for managing stress, and yoga modules have proven effective as sole or adjunct therapies in psychiatric disorders such as **anxiety, depression** and even **psychosis** (da Silva et al. 2009)(Varambally & Gangadhar., 2012).

**Meditation and mindfulness:** Meditation has been practiced since ancient times as a component of numerous spiritual traditions. The word meditation is generally used for a variety of practices aimed at focusing awareness and attention to voluntarily control mental processes (Marchand, 2013). Meditation is an extremely complex process, and more than one function is responsible for its effects. Many different practices of meditation have existed across cultures, including Hinduism (Transcendental meditation, Kundalini meditation, also see *yoga*), Islam (*Tafakkur*), Sikhism (*simran*), Christianity (*contemplative prayer*) and the **Tibetan meditation** (*rig pa cog bzhag*). Transcendental Meditation became very popular after it was introduced to the West by Maharishi Mahesh Yogi, a scholar of the ancient Vedic tradition of India. The technique is simple and easily learned, requiring to be practiced for 20 minutes twice daily while sitting with eyes closed and repeating a ‘mantra’, a sequence of specific sounds, to promote a natural shift of awareness to a wakeful but deeply restful state. A reduction in mental and physical activity occurs, a mental state called — transcendental consciousness, which is different from usual waking, dreaming, or sleep states. This experience is deemed responsible for the restoration of normal function of various bodily systems, especially those involved in adapting to environmental stressors or challenges. Regular practice of transcendental meditation improves brain functioning, attention and cortical coherence. Clinical effects include reduced **anxiety, pain, and depression; enhanced mood and self-esteem, and decreased stress** (Varvogli & Darviri., 2011).

**Mindfulness or Reality-directed Observation:** This originates from Buddhist philosophy and approaches such as *Vipassana* (often translated as “insight”). In modern sources, the approach is also referred to as “**awareness meditation**” or “**mindfulness**.” Its cultivation is described as conducive to full understanding of the three essential characteristics of all conditioned phenomena: **impermanence**,

**suffering, and no(n)-Self.** The latter implies that one's physical and mental constituents do not represent the eternal Self or belong to oneself forever.

Mindfulness is the process of attending to present moment sensations and experiences with a **non-judgmental stance**. Mindfulness decreases ruminations and worry, and impacts symptoms of depression and anxiety through both distinct and common emotion regulatory mechanisms(Desrosiers et al. 2013). Mindfulness-based stress reduction and mindfulness-based cognitive therapy have been studied as clinical interventions and have strong evidence documenting their effectiveness in **stress-related psychiatric disorders**.

**Tai chi & Qigong:** *Tai chi chuan* or *tai chi* is designed to increase the life force in the body through a series of slow circular movements. It is a **moving form of meditation** and is based on the search for perfect balance between yin and yang energies. Chinese *Qigong* has been practiced for more than 2000 years. ***Qigong means the skill or work (gong) of cultivating energy (Qi)***. ‘*Still*’ *Qigong* is practiced as a motionless meditation with the emphasis on breath and intentional thoughts. ‘*Moving*’ *Qigong* involves external movements under the conscious direction of the mind. Both *Tai Chi* and *Qigong* involve sequences of flowing movements coupled with changes in mental focus, breathing, coordination, and relaxation. Both practices have a significant overlap of technique and are low-impact, moderate intensity aerobic exercises that are suitable across different age groups and health conditions. They are practiced worldwide in a variety of modern and traditional forms. However, many RCT’s have used the Yang style or the Yang style short form to study the effectiveness of this practice.

*Tai Chi* and *Qigong* have been shown to have various salutary effects on the autonomic system, immuno-inflammatory system, and the hypothalamic–pituitary–adrenal (HPA) axis (Abbott & Lavretsky, 2013). EEG studies have shown increased frontal  $\alpha$ ,  $\beta$  and  $\theta$  activity, suggesting increased relaxation and attentiveness. RCT’s have shown that *Tai Chi* and *Qigong* may improve bone density, cardiopulmonary health, arthritis, fibromyalgia, tension headaches, and other medical conditions. It is associated with improvements in psycho-social wellbeing including reduced **stress, anxiety, depression**, increased self esteem, and improvement in health-related quality of life (HRQOL). It improves sleep quality, **improves balance and reduces falls**, owing to which it has been recommended as treatment of **mild depression in geriatric population**. *Tai Chi* also seems to reduce balance

impairments in patients with **mild to moderate Parkinson disease**. In patients with **substance use disorders**, *Qigong* participants experienced a higher treatment completion rate, improved anxiety scores, greater reductions in cravings and lower relapse rates. Patients with **traumatic brain injury** also had improved mood and self-esteem after *Qigong*, with improved HRQOL.

## ENERGY-BASED THERAPIES

The concept of subtle energy and methods of its use for healing has been described by numerous cultures for thousands of years. These vital energy concepts (which include the Indian term *prana*, the Chinese term *chi*, and the Japanese term *qi*, all refer to so-called **subtle or non-physical energies** that permeate existence and have specific effects on the body-mind of all conscious beings. Similar concepts in the West are reflected in the concepts of Holy Spirit or spirit and can be dated back to writings in the Old Testament as well as the practice of laying-on of hands. According to the National Institute of Health (NIH), energy-based therapies “**are intended to affect energy fields that purportedly surround and penetrate the human body.**”

Despite differences in ontologies of these proposed forces, a common thread is the techniques that attempt to use subtle energy to stimulate one’s own healing process. These are clearly reflected in internal (intrapersonal), movement-oriented practices described above such as *yoga*, *tai-chi*, and internal *qigong*, and are often noted as part of the experience of meditation and prayer. In addition, different cultures have developed **external (interpersonal) practices** that purport to specifically use subtle energies for the process of healing another. These include local or proximal practices such as external *Qigong*, *pranic* healing, and laying on of hands, where a healer transmits or guides energy to **a recipient who is physically present**; as well as distance practices where a healer sends energy to a recipient in a different physical location, such as **intercessory prayer or distance healing**. Thus, the energy-based therapies share in common: 1) the idea that the therapeutic effects rest on **manipulation of some energy fields** associated with the human body; and 2) the manipulation of that energy is done by a **therapist**, with the **patient** as passive participant.

**External *qi* Therapy (External *Qigong*):** Persons who have mastered their own practice of *qigong* are considered to be able to cultivate the ability to emit *qi* and

thus direct it therapeutically to the disturbed energy fields of other people. This is believed to help patients “clear *qi* blockages, expel negative *qi*, and balance the flow of *qi* in body. Though few definitive conclusions can be drawn, studies have shown positive effects on **anxiety and depressive symptoms**, as well as reduction in **pain severity**.

**Reiki:** *Rei-ki* is a Japanese word with the general meaning of “healing” (*Rei* means “universal” or “spiritual” and *Ki* is “life force energy”). It is a Japanese form of hands-on healing in which a certified practitioner places his or her hands on or near the head, throat, chest, abdomen, knees, and feet of an individual to redistribute stagnant energy.

There are two degrees of *Reiki* healing as follows:

- **First degree** *Reiki* practitioners use light, non-manipulative touch to precipitate a flow of healing energy, called *Reiki*, drawn through the practitioner and into the patient according to the recipient’s needs.
- **Second-degree** healing enables practitioners to access this energy for distant healing when touch is impossible.

*Reiki* is one of many methods that are part of Chinese family of Qigong and are used to activate, harmonize, and reconnect the self with the universal energy. It has its roots in ancient Buddhism/ Shintoism, but differs from the common stream in one central point: the energy is transferred or made available to the student by initiation, not by years of long practice. It was rediscovered by Mr. Mikao Usui of Kyoto, Japan, towards the end of the 19<sup>th</sup> century, and it was he who named it *Rei-ki*. It is believed that *Reiki* not only heals diseases, but also amplifies innate abilities, balances the spirit, makes the body healthy, and thus helps achieve happiness. There is indeed some suggestive evidence that *Reiki* can influence **mood** and induce physiological change in humans and animals.

*Reiki* is often listed with other Bio-field therapies, viz. therapeutic touch, and healing touch as a form of complementary medicine practice. There is moderate to strong evidence for effects of biofield therapies in **decreasing pain intensity**. There is also moderate evidence that it helps reduce **negative behaviours associated with dementia** and decreases **anxiety** in hospitalized populations (Jain & Mills., 2010).

**Acupressure and Acupuncture:** Traditional Chinese medicine has been used to treat mental illness since 1100 BC. A basic tenet of Chinese medicine is that energy (*qi* or *chi*) flows along specific pathways (meridians) that have about **350 major points (acu-points)** whose manipulation corrects imbalances by stimulating or removing blockages to energy flow. Another fundamental concept is the idea of **two opposing energy fields (yin and yang) that must be in balance** for health to be sustained. In acupressure, the pressure points are manipulated by the fingers; in acupuncture, sterilized silver or gold needles are inserted into the skin to varying depths and are rotated or left in place for varying periods to correct any imbalance of *qi*. The needles may be manipulated manually or stimulated by electrical impulses. Other techniques such as **moxibustion** (burning small cones of dried, powdered *Artemisia vulgaris* (moxa) leaves held above the point to be warmed or placed on the skin and removed before overheating occurs), pressure, heat, and laser are also used.

In traditional practice of acupuncture, a practitioner plans a series of sessions utilizing unique acupuncture points for each patient based on the individual constitution of the patient. The effects of acupuncture which are largely sympatho-inhibitory in animals and humans, is dependent on needle location and acupuncture type. It may be mediated largely through neurotransmitter systems in an opioid-dependent manner. The opioid system is hypothesized to be aberrant in anxiety and stress-related disorders. Manual acupuncture causes a broad matrix of central neurological responses involving the amygdala, hippocampus, hypothalamus, cerebellum, basal ganglia, anterior cingulate, insula, and other limbic structures as seen on functional magnetic resonance imaging, positron emission tomography and EEG (Hollifield et al., 2007). The response in various CNS targets is dependent on the type of acupuncture and the frequency of stimulation in the case of electro-acupuncture.

A variety of medical conditions may benefit from the use of acupuncture or moxibustion. These include prevention and treatment of **nausea and vomiting**; treatment of **pain** and **addictions to alcohol, and illicit drugs**; pulmonary problems such as **asthma and bronchitis**; rehabilitation from neurological damage such as that caused by **stroke**. It also may be efficacious for reducing symptoms of **PTSD, depression, anxiety**. Studies from China using electro-acupuncture, laser-acupuncture, auricular acupuncture or scalp acupuncture for the treatment of **hallucinations**, and He-Ne laser irradiation of acu-point have provided preliminary

evidence that acupuncture may help reduce the dose of antipsychotics in patients with **schizophrenia** (Kiresuk & Trachtenberg., 2005).

## BODY-BASED/ MANIPULATIVE THERAPIES

Methods of spinal manipulation have dated back to times of Hippocrates and Galen. Acupressure, as described above, would also fit in this sub-class of CAM treatments. Massage, as a form of therapy, is described below.

**Massage:** Massage is a treatment that involves manipulation of the soft tissues and the surfaces of the body. It was prescribed for the treatment of disease more than 5,000 years ago by Chinese physicians, and Hippocrates believed it to be an important **method of healing**. Archaeological evidence of massage has been found in many ancient civilizations including China, India, Japan, Korea, Egypt, Rome, Greece, and Mesopotamia. Sanskrit records indicate that massage had been practiced in India long before the beginning of recorded history. It is said to increase blood circulation, to improve the flow of lymph, to soothe sore muscles, and to have a tranquilizing effect on the mind.

Various massage techniques have been described: **stroking, kneading, pinching, rubbing, knuckling, tapping, or applying friction**. Massage is most often done with the hands and fingers, but vibrating machines and electrical stimulation are also used. Many different styles of massage are used in modern-day practice such as Swedish, Thai, Oriental, Tantric, Balinese, Shiatsu, Ayurvedic massage etc. Besides being used by indigenous practitioners, these also have become a trending pattern in modern day recreation centres like Spas, ‘wellness centres’ and ‘Organic resorts’. Massage therapy is believed to stimulate the parasympathetic branch of the autonomic nervous system and have a beneficial effect on several physiological variables, specifically salivary cortisol and heart rate. Studies have proved massage to reduce **anxiety and pain perception** (Moraska *et al.* 2010). Learning the practice of infant massage by mothers is an effective treatment for facilitating mother-infant interaction in mothers with postnatal depression. Clinical research in this area is too preliminary to make definitive statements about its efficacy in reducing stress in any particular patient population.

## WHOLE MEDICAL SYSTEMS

**Ayurveda** is a technique that originated in India about 4000 BC and is believed to be one of the most comprehensive medical systems on the world. It is similar in its beliefs about the energy points on the body and a vital force (*prana*) that must be in balance to maintain health. It bases diagnosis on examination of pulse, urine, warmth or coldness of body, and for treatment uses diet, medicines, purification, enemas, and in some cases, blood-letting. Current forms of this medical system show Buddhist and Hindu contributions and are highly respected, involving considerable medical training from recognized Ayurvedic medical schools all over India and some other countries. Ayurvedic concepts may be applicable to conditions such as **anxiety, neurosis, and depressive disorders**.

Modern **Chinese medicine** relies on herbs in addition to other methods such as acupuncture, massage, diet, and exercise, to correct so-called imbalances in the body. The Tibetan health system is as old as the 7<sup>th</sup> century AD, and has elements of Arabic, Indian, and Chinese health systems, with its practice closely related to religion and magic.

**Homeopathy** was developed in the early 19<sup>th</sup> century by Samuel Hahnemann, a German physician. Its pharmacopoeia has more than 2000 medicines, and medications are derived from plants, minerals and animals, while they are dispensed as tinctures or pills with lactose fillers in infinitesimally dilute solutions. The selection of medicine is based on the law of similars; *—Similia similibus curantur* (let like be cured by like). For instance, a medicine which produces nausea would be used in minute concentrations to treat nausea.

Other health systems such as **Siddha, Unani, Balinese medicine**, and various forms of tribal medicine are practiced in circumscribed parts of the world.

## OTHER TRADITIONAL HEALING PRACTICES

One must not forget various **supernatural and natural therapies** that have been witnessed and experienced by generations in history among different cultures. In various forms of supernatural therapies, the therapeutic goal is achieved through the ritual of prayer, testimony, sacrifice, reliving experience, or even spirit possession. Healing mechanisms used in these practices are assurance, suggestions and generation of conviction. Some examples would be Shamanism, Zar ceremonies, spirit dancing ceremony, Christian religious healing, etc. The pervasive interest in

**faith healing**, the curative anecdotes of television evangelists and spiritual gurus, and the millions of hopeful individuals visiting religious shrines in search of relief give witness to the continuing interest in and prevalence of prayer and spirituality in the process of healing.

There are several clinical reports and reviews advocating the use of **shared prayer, silent prayer, and distant prayer in nursing care**. There is a large body of epidemiological research that indicates that religious beliefs and practices are negatively correlated with substance abuse and positively correlated with health status (Chatters, 2000). Also, programs like the 12-step program of **Alcoholics Anonymous** have successfully incorporated prayer and spirituality in the treatment of addictive behaviour. Subjects receiving religion-based cognitive behavioural therapy do better, regardless of the religiosity of the therapist conducting the therapy. Personal belief in religion and active attendance at worship has been correlated with a moderately decreased incidence of depression and hypertension (Ellison, 1994)..

The core and effectiveness of different methods of religious and magical healing seems to lie in their ability to arouse hope and the innate healing ability in the individual. The folk-healing practices and modern psychotherapy share a number of non-specific therapeutic mechanisms.

## **CONCLUSIONS**

Stress is a near-universal experience. Several traditional healing practices used for relief from stress and associated problems have been discussed above. Although most evidence-based practices have been included, the reader will acknowledge that it is difficult to cover all such practices in a single chapter. It is important for the practicing physician or indeed any healer, to understand and selectively incorporate elements of traditional methods into practice, based on patient understanding and expectation. Regardless of diagnosis, it is important to view the patient holistically and emphasize treatment of the individual as a whole rather than the illness or condition.

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## **STRESS AND PSYCHOLOGICAL FIRST AID**

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### **OUTLINE**

- |  |                                    |
|--|------------------------------------|
| 1. INTRODUCTION                          | 2. WHO CAN PROVIDE IMMEDIATE CARE? |
| 3. COMPONENTS OF PSYCHOLOGICAL FIRST AID | 4. WHY MENTAL HEALTH FIRST AID?    |
| 5. CONCLUSIONS                           |                                    |

## **INTRODUCTION**

Mental health disorders contribute significantly to the global burden of disease. The world needs to focus on the growing numbers across the globe to actively intervene. Mental and behavioural disorders account for about 12% of the global burden of diseases. This is likely to increase to 15% by 2020. At least one in four families has at least one member currently suffering from a mental or behavioural disorder (Murray & Lopez, 2000). These families are required not only to provide physical and emotional support, but also to bear the negative impact of stigma and discrimination that they face because of their family members suffering from a mental health disorder (Pai & Kapur, 1981; Fadden et al., 1987; Winefield & Harvey, 1994).

With an increase in the rate of mental health disorders across the communities, there is a significant treatment gap and lack of awareness among the public about mental health disorders. Adding to that, a lack of awareness on the various treatment

options and when can one refer the person to the mental health professional is limited. Although there are both pharmacological and psychosocial treatments available, lack of knowledge regarding the same has resulted only in few accessing them.

While some of us are able to cope effectively from a mental health crisis, it's been observed that many may have difficulty. Some people may have mild response which can be addressed effectively through active interventions, whereas others may have severe response to the crisis warranting an admission to an emergency care set up.(Jorm et al., 1997). There may be many factors which can predispose an individual to develop a mental health crisis and how he or she responds to it. Active support from family, community, gender, cultural background and personality characteristics can significantly predict the outcomes.

If one is suffering from mental health issue, it can manifest as negative emotional states like anger, irritability, and fear, to name a few. Generally, friends and family members can have difficulty in identifying a person who is undergoing a mental health issue. They might be aware that something is not right, but feel helpless in providing aid. It may be often due to lack of awareness of various mental health problems and how one needs to respond. Availing the existing services for getting better may not be considered as the first option, and delay in recognition and treatment could lead to worsening of the mental health issue. As a society, we are, and continue to be ignorant, of the mental health issues that our communities are facing. Through active intervention at an early stage, these problems can be prevented from escalating to the problem being diagnosed as a mental health condition. Thus, it is of utmost importance to gain the knowledge and skills to provide immediate care, as a first hand support to people facing a mental health crisis.

Every member in the community is a strong force to reckon wherein they can play many crucial roles in early identification of people facing a crisis. They can play a role in early recognition of the symptoms of mental illness, provide support and, encourage to seek appropriate professional help. We need to involve the members of the community in actively training them as they are the first point of contact, as a key stakeholder. Various training programs have been initiated in different countries across the globe for the public which have met with considerable success.

The concept of Psychological and Mental Health First Aid has been there for many decades, but has garnered momentum and interest only in the past two decades. During the World War 2 and its after effects, there was a growing concern raised around people who suffered from mild to moderate cases of mild mental health problems. This led to thinking as to how it can be managed and prevented. A plan of action was developed in 1945 to address these issues (Blain et al., 1945). However, owing to stigma surrounding around mental health problems and those affected with it, it did not gain the importance it deserved.

Awareness regarding first aid for mental health was in its infancy until the concept of mental health literacy started doing the rounds in the 1990s which led to the development of a Mental Health First Aid training course that evaluated in Australia in 2002 (Kitchener & Jorm, 2002). MHFA training is a structured program or a brief course available for the members of the community. It teaches them as to how they can assist someone who is developing a mental illness or experiencing a mental health crisis situation (e.g. if the person is having feelings of sadness or having an acute psychotic symptoms). This first aid is continued until the person receives appropriate help from a mental health professional or until the he or she has taken appropriate steps to resolve the crisis.

## **WHO CAN PROVIDE IMMEDIATE CARE?**

It can be anyone who assists a person in need of psychosocial support, during or after a distressing or crisis event. These include:

- Relatives or Family members
- Neighbours
- Teachers
- Community members
- Emergency medical teams
- Mental Health Professionals
- Counsellors
- Police
- Non-Government Organization
- Members at workplace

## COMPONENTS OF PSYCHOLOGICAL FIRST AID

The Mental Health (Psychological) First Aid program focuses on empowering the community with skills that are needed to address someone facing a mental health issue in the community. The course teaches the community member how to give mental health first aid using a five-component MHFA Action Plan (Kitchener, 2015).

**Table 1: Action plan for psychological first aid**

Action Plan 1	Identify the person facing a mental health crisis and develop rapport and approach the person
Action Plan 2	Understand the mental health disorder/crisis he or she is facing
Action Plan 3	Adopt basic listening skills and maintain confidentiality by providing adequate support
Action Plan 4	Refer to a mental health professional if required
Action Plan 5	Strengthen their support systems

WHO in its systematic review (2012) supported the concept of Psychological First Aid and the training package for the community. They have stressed that many people who suffer from various mental health problems, and those suffering from mental health disorders can benefit by trained members from the community.

Statistics says every one in four adults will experience a mental health crisis in their lifetime. Owing to acute shortage of mental health professionals, access to care and societal prejudices, many may receive little or no treatment. People respond differently to mental health crisis because of ignorance, poor knowledge, stigma and discrimination (Fox et al., 2012).

Many countries across the globe have redesigned the MHFA course for the members of their community and its effectiveness have been evaluated. Meta-analysis of 18 controlled trials by Bisson & Lewis (2009) found that it was effective up to 6 months post the training, with improvement in knowledge of mental health disorders, recognition and identification of mental disorders and availability of treatments (Bisson & Lewis, 2009). Improvements were also observed in community members confident about providing mental health first aid. Hence, it can be reiterated that there are adequate documented evidence that MHFA training improves mental health literacy with in the community and how through a

structured training program, the members can become key advocates in providing care to those affected.

As the MHFA training gained momentum, lot of consideration was given to focus on specific populations at risk for mental health disorders and targeting specific disorders. Redevelopment of the mental health first aid guidelines were aimed for Persons suffering from traumatic event, non-suicidal self-injury, depression and those having suicidal ideation and behaviour.

A Delphi study was conducted to incorporate supportive statements for the guidelines for members who were undergoing training (Chalmers et al., 2020). This study came out with a set of guidelines than the original version, with 103 encouraging statements and helping actions. The additional guidance on providing initial assistance, talking about the trauma, offering short-term assistance and seeking appropriate professional help reflects current knowledge. A noteworthy addition is also as to how a first aider can assist after a disclosure of abuse.

Delphi consensus method to determine the importance of including helping statements in the guidelines for suicidal ideations and behaviour was undertaken (Ross et al., 2014). They describe as to the action a member of the public can take, and how they can help someone who is experiencing suicidal ideations. Systematic searches of the available suicide prevention literature were carried out to find helping statements. Two expert panels, comprising of 41 suicide prevention professionals and 35 consumer advocates respectively, rated each statement. 164 redesigned statements were endorsed by the expert panel as appropriate helping actions in providing assistance to someone experiencing suicidal thoughts or engaging in suicidal behaviour.

Delphi method looked into how members of the public can provide mental health first aid to someone who is experiencing depression (Bond et al., 2019). A survey method was adopted using the 2008 depression mental health first aid guidelines and a systematic search was followed. This re-development added detail to the previous version of the guidelines, giving more guidance on the role of the first aider.

Most of the above MHFA course focuses on training community members on mental health disorders. There is hardly any training programs conducted for the

community on identifying day to day stress that people face which can lead to a mental health crisis. One such unique initiative was adopted at National Institute of Mental Health and Neuro Sciences [NIMHANS], Bengaluru, India in 2016 namely providing “Immediate care for Psychological events and Emergencies”. So far, more than 5000 people have been trained from all over the country. A three hour training program was conceptualised for the public to enhance their skills to reaching out to people who could be facing a mental health crisis (Murthy et al., 2019). This initiative adopts a different methodology from the other first aid training programs which are being carried out globally. The focus of this program is to explore and enhance the knowledge of mental health problems within the member and build his or her skills needed to intervene, reach out, assist, and refer individuals experiencing a mental health crisis for various instances. A life cycle approach is carried out to understand what could be the possible mental health crisis an individual is at risk for facing at a particular life stage. The training program has set up to be a successful model and a pilot training of trainers was carried out with a objective of having more such initiatives. The success of the program stems from the training that it is easy to comprehend, identify a crisis before it turns chronic or develops into a mental health disorder, as well as the person affected having complete insight and able to work around the issue constructively.

The training program was recently redesigned to train public in identifying the mental health crisis that people faced during the COVID-19 pandemic. The emergence of COVID-19 pandemic and its rapid spread have brought about a huge psychosocial impact on our mental health. People are getting anxious due to nature of rapid spread of illness and its cause is uncertain. Besides, anxiety among people in communities have risen because of the unprecedented quarantine measures and physical distancing adopted by the Government to contain the pandemic. Adding to that, media reports, particularly ‘infodemic’ or misinformation or fake news from social media, on increasing number of cases in a particular region or among particular caste or religious groups, lack of availability of health services and personal protective equipment’s, unforeseen shortage of supply or price rise of grocery essentials, future economic crisis associated to the COVID-19 crisis, has perpetuated the fear and anxiety among communities. People are feeling overwhelmed, confused and uncertain about what is happening.

People in crisis have been ill prepared to deal with the circumstances which is unexpected and thereby have become anxious. Added to this, the pandemic has

enforced government rules like social distancing and self-isolation which has made the person vulnerable to increased stress. Prolonged stress and anxiety can worsen leading to chronic psychological and physical problems, increase disability and have negative effects on family dynamics, critical-making, ability to take decisions, interpersonal relationships and their day to day functioning. The mental health and psychosocial response to a pandemic is significant. Social support and sustained attachments to loved ones and social groups can help them in addressing anxiety and in enhancing their health during this time. Thus, it is of utmost importance to gain the knowledge and skills to provide immediate care, as a first hand support to people with mental health issues.

## WHY MENTAL HEALTH FIRST AID?

**Table 2: Reason and justification for mental health first aid**

No	Reason	Justification
1	Mental health problems are common to all	Research has well documented that anyone can be at risk for developing a mental health disorder, irrespective of age, gender, race, or socio-economic status.
2	Myths and Misconception are high	Every society across countries has various myths surrounding, which makes stops people from accessing treatment and care. These need to be addressed and corrected.
3	Stigma and Discrimination	The stigma around Persons suffering from mental health disorders is very evident. It stops the person from accessing to health care needs, his or her basic rights, job opportunities and to lead a life with dignity.
4	Poor insight	The person suffering from a mental health problem at times may not have an insight that he or she is going through a crisis and may tend to normalize it.
5	Access to healthcare	Insufficient knowledge with regards to accessing mental health professionals who can help a Person facing a mental health crisis is limited.
6	Community is a key stakeholder	We have been talking of community as a key partner in identification and reaching out to the person affected. Every individual has a inherent tendency to comprehend when another person is in distress. Equipping him or her with additional skills of helping someone in distress can minimise the distress and the community can function as a unit.

### Key takeaways

- Equip yourself with skills to provide basic psychological and mental health first aid so that you can reach out to anyone facing a mental health crisis
- Address the stigma faced by persons suffering from mental health problems and their caregivers
- Empower the Persons suffering from mental health problems to live with dignity and grace
- Educate others that like physical health, mental health is very important and both are integrated.
- Understand the cultural background and be sensitive to the needs of the Persons suffering from a mental health issue

## CONCLUSION

Early identification of symptoms of mental illness and psychological emergencies is key for better outcome for treatment or for the therapies. However, due to paucity of human resources and non-availability of contextually appropriate interventions, vast majority of the who need psychological help remains untreated. In countries deprived of resources and access to treatments, initiating or adopting newer methodologies has been an effective approach to addressing the treatment gap and lack of mental health professionals (Javadi et al., 2017; Eaton et al., 2011; Kakuma et al., 2011; Patel et al., 2010). Task shifting includes shifting service delivery of specific tasks from professionals with higher qualifications to those with fewer qualifications or creating a new cadre with specific training (WHO, 2007b). In addition, the community needs to be literate on mental health in order to identify early symptoms and psychological crisis and to link patients to the health care system. The first-aid for the psychological emergencies is one such model, which used gatekeeper approach which intended to improve knowledge among the lay-people on various psychological crisis, thereby improve help seeking for their psychological crisis. In accordance with the existing evidences, we found our programme was effective in improving participants' knowledge and skills. However, there is paucity of evidence with regards to changing participants' attitudes and gatekeeper behaviour. There is need to develop contextually relevant

and culturally appropriate training module on various psychological emergencies to reach the unreached across the communities and various vulnerable population.

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## **STRESS AND TELE-PSYCHIATRY**

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## **INTRODUCTION**

Psychosocial stress is a pervasive problem in the health care system due to its role in the aetiology and prognosis of multiple physical and mental health conditions (Schneiderman et al., 2005). It affects medication adherence, predicts poorer outcomes, and adds to the financial burden of disease. Telepsychiatry has the potential as an accessible, ubiquitous, and real-time stress management tool, that can reduce overall disease burden (Wang et al., 2018; Davies et al., 2004). In this chapter, we hope to elucidate the modes of telepsychiatry, its application to stress management, and its limitations and challenges in contrast to hospital-based care.

## **TELE-PSYCHIATRY AND STRESS**

Telemedicine is defined as the practice of medical care using interactive audio, visual, and data communications. These programs cover various disciplines of medicine such as radiology, dermatology, medicine, and including psychiatry.

Telepsychiatry is one of the most promising and upcoming applications of telemedicine in the world. Even in developing countries, telepsychiatry is picking up momentum (Naskar et al., 2017). Second Global Survey on eHealth by the World Health Organization in 114 of its member states showed that 24% countries had telepsychiatry (13% established ones); of which <10% in low and middle income countries (WHO, 2009). In next five years, the Third Global Survey on eHealth by WHO in 125 of its member states showed 34% of member countries had telepsychiatry (25% established ones) (WHO, 2016).

Other terms for telepsychiatry include “e-mental health” or “Tele-mental health”. It is defined as the use of information and communication technology to provide and support psychiatric services. The term telepsychiatry was first used by Dwyer to describe consultation services provided from Massachusetts General Hospital to a medical site in Boston. Telepsychiatry can be used for clinical evaluation, diagnosis and management, education, and research purposes. Therefore, it has the potential to be both an afferent and efferent arm of clinical care in various disorders such as depression, anxiety disorders, schizophrenia, eating disorder, and post-traumatic stress disorder (Wang et al., 2018; García-Lizana & Muñoz-Mayorga, 2010).

H. Selye defined stress as “Nonspecific response of the body to any demand for change”. However, his definition described only the physiological effects of stress and failed to discuss the psychological component to it (Selye, 1956). Lazarus and Folkman’s definition of stress included psychological dimensions to it and suggested that stress occurs when people perceived that the demands from external situations were beyond their coping capacity (Lazarus & Folkman, 1984). Stress can have adverse consequences on physical health, cause burn out, precipitate psychiatric illness, and causes significant dysfunction in social and occupational domains thereby its management is of immense urgency. Telepsychiatry, due to its anonymity, portability, and ease of access could offer an effective mode of assessing and managing stress. It also provides an alternative in areas with poor access to mental health services and unequal distribution of mental health resources with urban-rural discrepancies (Radovic et al., 2016; Rathbone & Prescott, 2017).

Telepsychiatry can be useful for assessing and delivering the intervention in populations with increased stress such as occupational stress, students, chronic medically ill patients, and people with stress-related psychiatric disorders. Among people with physical illness telepsychiatry has been useful in improving

depressive and anxiety symptoms and has been extensively studied in irritable bowel syndrome, cancer, chronic pain, fibromyalgia, recurrent headache and hypertension (Mikolasek et al., 2018).

## **MODELS OF TELE-PSYCHIATRY**

There are two modes of communication described in various models of telepsychiatry,

### **1. Synchronous**

It is also called as interactive communication. It comprises of living, two-way communication between the patient and the doctor. It includes telephone consultations, online communication via chat forums, and videoconferencing. It has the advantage of the possibility of immediate response and is closest to “face to face” interaction. It is however limited by the quality of the technology accessible to the patient and doctors.

### **2. Asynchronous**

It is communication wherein both parties are not present at the same time and is a type of “Store and forward” interaction. Here the information is collected, stored, and forwarded to the specialist for review. It could be in the format of audio, video, and questionnaires. The advantage of this is that the technology is relatively simpler, more inexpensive, and more accessible (Malhotra et al., 2013).

## **TELE-PSYCHIATRY FOR STRESS EVALUATION AND ASSESSMENT**

Telepsychiatry services used for stress evaluation include video-conferencing, app-based assessments, and intervention, computer/ internet-based interventions. Both synchronous and asynchronous modes of communication have been used in stress management. The traditional model of consultation is where the psychiatrist provides the health care services directly via the above mentioned methods to the patient. The consultation care model is where the primary care physician is the principal provider and collaborative model includes both the psychiatrist and primary care physician in providing the services.

General recommendations for teleconsultations have been issued in May 2020, by the Indian Psychiatric society and Telemedicine society of India in collaboration

with the National institute of Mental Health and Neurosciences, the “Telepsychiatry operational guidelines” gives practical advice aimed to assist in implementation of telepsychiatry services.

Scales used to assess stress severity over telepsychiatry include the Perceived Stress Scale (PSS) and Visual Analogue Scales (VAS) for assessing stress and anxiety. In the research settings most commonly used scales to assess stress in telepsychiatry include the PSS and the Depression, anxiety, stress scale (DASS) scale (Davies et al., 2014). PSS is the most widely used 10 item scale. It measures the severity of a person’s perception of situations in life as stressful (Lee, 2012). The DASS is a 42-item self-report instrument designed to measure the three related negative emotional states of depression, anxiety, and tension/stress. The DASS questionnaire is in the public domain (Parkitny & McAuley, 2010).

## **MOBILE APPS BASED INTERVENTIONS FOR STRESS**

Stress management strategies include common principles of relaxation such as diaphragmatic breathing or progressive muscle relaxation, meditation, mindfulness-based interventions, guided imagery and visualization, cognitive behaviour therapy, seeking social support, etc. There are over 900 applications that claim to deliver these interventions. It is found that the most common strategy used is mindfulness and meditation, followed by applications that guide relaxation exercises like diaphragmatic breathing. Some applications provide platforms for safe seeking of social support as well as use guided imagery to achieve a state of relaxation. Components of cognitive behaviour therapy are frequently delivered via these platforms such as behavioural activation, cognitive restructuring, and problem-solving approaches. These applications also offer components of psycho-education and encourage self-monitoring of symptoms.

While the majority of the applications justify within the applications that support the claims of stress management, most currently do not provide references for that information. Other important aspects to be remembered while advising these applications include whether the application was developed by competent authorities, ensures confidentiality, provides contact information for app managers and has clear financial disclosure.

In terms of the acceptability of the user interface, the size of the applications ranges from 1.1 MB to 396 MB with a median of 28.5 MB. Currently, both free

and paid versions of the apps exist and are available across multiple platforms such as android and iOS.

Examples of some smartphone applications with evidence based strategies for stress management are-

1. Giant mind app is a free application based on mindfulness and meditation available across various operating systems.
2. Address stress app is based on deep breathing and progressive muscle relaxation and offers a self-supported 14 day stress relaxation program.
3. Breathing room app uses guided imagery and mindfulness based principles
4. Mood kit and Stress Management are the two paid applications that attempt at stress management via cognitive restructuring, improving coping and promote seeking social support.

Other common applications include Headspace, Tension Tamer, Virtual Hope box etc. (Radovic et al., 2016; Rathbone & Prescott, 2017).

In managing specific stress related mental disorders such as PTSD in veterans, an app- PTSD coach has been studied. The app can be self-managed or clinician managed. The participants in the study found the app helpful in managing their PTSD symptoms (Rathbone & Prescott, 2017).

## **COMPUTER DELIVERED AND WEB-BASED INTERVENTIONS FOR STRESS**

Computer-based assessment and management can be done with technology such as video conferencing, emails, and blogs. It can be done online or via offline programs. They have many advantages such as an easy, anonymous, and private platform for conveying sensitive information. It can also be used for education and training purposes in remote areas. Interventions via these platforms can be more general such as improving social support, promoting general psychological and physical wellbeing for stress management as well as specific stress-related disorders such as post-traumatic stress disorder (PTSD) and acute stress reactions. The principles of these interventions are rooted in cognitive behaviour theory, mindfulness-based therapies, stress management theory, and cognitive learning theory. Most

interventions range from 2 to 12 weeks in duration and each session lasts between 30 to 120 minutes each. They can be self-administered or in a semi-guided format. In the semi-guided formats emails are often sent to the clients for reminders and to assess progress. In most studies, the participants belong to younger age groups, indicating a preference for this modality of intervention to the youngsters.

The interventions use text, audio, video, graphics, and animations and some also offer interactive platforms, E.g., SMART-OP and MoodGym applications included interactive activities and online workbooks. Most of these programs have been self-reported to be moderately helpful in managing stress (Davies et al., 2014).

Computer based psychotherapy has been proven effective for the management of PTSD. It has been found effective in all age groups including elderly and children, in both rural and urban settings. The various traumatic triggering events studied include war (veterans), natural disasters, and postpartum periods. Veterans are at-risk populations for PTSD but stigma and geographical barriers prevent their engagement in evidence-based treatment programs. Computer-based videoconferencing technology has been used for delivering cognitive behaviour therapy, group psychotherapy, and exposure therapy with promising results in comparison the face to face psychotherapy. Studies on Eye movement desensitization reprocessing are lacking. One study suggested that telepsychiatry based collaborative care can improve engagement in cognitive processing therapy, prescription of prazosin, and overall better outcomes in veterans. In a systematic review, follow up data ranged from 5 weeks to up to 18 months, showed that quality of care delivered via videoconferencing as well as web and application-based intervention is comparable to face to face intervention. An added advantage was that the therapeutic time was lesser than face to face therapy. For PTSD post natural disasters, web-based application called “My trauma Recovery” has been proven effective in PTSD in earthquake victims in China (Sunjaya et al., 2020).

Early research into the management of acute stress disorder in war deployment zones has begun. Successful management of one case study by exposure therapy via videoconferencing has been reported (Pelton et al., 2015).

### **Digital Phenotyping for stress management**

Digital phenotyping is defined as the ‘moment-by-moment quantification of the individual-level human phenotype in situ using data from personal digital devices’.

It uses data of activity, GPRS location, number of messages or emails, keyboard usage patterns, and voice analysis. It is more objective than traditional clinical evaluation based on subjective patient reports and universally available with the increasing trend in use of mobile phones. It can passively and continuously assess in real-time basis in the patient's life in contrast to clinical assessment in hospital settings at follow-ups (Huckvale et al., 2019).

Digital phenotyping can help in stress management by passive assessment of changes in self-perceived stress which can be used to teach self-regulation and resilience or encourage seeking help before worsening of symptoms or onset of more serious mental illness. Apps under study for Digital phenotyping for stress are DeepMood, EmotionCheck and i-Care Stress app. DeepMood app assesses for mood, anxiety, and stress symptoms via mood log, behavioural log and sleep log. EmotionCheck app forecasts stress based on accelerometer sensors and pulse rate monitoring. I-Care Stress is another app that predicts stress via online surveys and questionnaires. It also has an intervention arm that operates via neurofeedback and relaxation therapy (Liang et al., 2019).

Among stress related mental disorders, the digital phenotype for the prediction, diagnosis and follow up of PTSD has not yet been conclusively identified although PTSD has been associated with decreased heart rate variability, increased skin conductance and sleep disturbances. GPS data could be utilised to detect avoidance behaviours (Bourla et al., 2018).

### **Digital biomarkers in stress research**

Biomarker is defined as “a characteristic that is objectively measured and evaluated as an indication of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.” A good biomarker should be objective, should have high reproducibility and sizeable signal to noise ratio. They can be classified as diagnostic, monitoring, pharmacodynamics/response, predictive, prognostic, safety, and risk biomarkers (García-Gutiérrez et al., 2020). Application of this concept to telepsychiatry, digital biomarkers could indicate mental status via the patients’ interaction and use of smartphones, biometric devices and other digital platforms. Common biomarkers studied are heart rate, actigraphy data, voice analysis and call/text frequency. There is mounting evidence supporting the ability of digital devices in detecting signs of stress via a wide array of digital biomarkers. For example, global positioning system(GPS) sensors can

identify movement patterns along with smartphone apps, which are able to collect passive data in the form of change in device or app usage and number of calls or texts. These digital biomarkers are associated with perceived stress and changes in mood in university population settings and neuropsychiatric populations.

Voice recordings from mobile devices can detect speed, pitch, pauses variations which are potential vocal markers of stress. Video data can do facial emotion recognition that correlate with subjective mood. Hence it is anticipated that these can be crucial in measuring stress and coping in the near future (Goodday & Friend, 2019). In a study of 59 patients of social anxiety disorder, passive data about patients' movement (accelerometers) and social contact (incoming and outgoing calls and texts) were collected over 2 weeks, and this could may accurately detect severity of symptoms of social anxiety and was able to discriminate this from depressive symptoms, negative affect, and positive affect (Jacobson et al., 2020). Existing mental health services, assessment mainly, are time consuming. Exploring and developing cost-effective, time-sensitive and scalable digital biomarkers for diagnosis, and for quantifying symptoms can be promising (Jacobson et al., 2019).

## **CHALLENGES IN IMPLEMENTING TELE-PSYCHIATRY FOR STRESS MANAGEMENT**

Currently, there are limited learning opportunities for clinicians in telepsychiatry. Lack of training in operating technology may reduce the therapist's motivation. It may add to the existing infrastructure and administrative barriers to implementing telepsychiatry. Therapists are often apprehensive about how technology may inhibit rapport building and decrease therapeutic alliance. Ensuring comfort of both the patient and physicians in the assessment nations and exposure is therefore limited. Further, given the absence of well-established guidelines for telepsychiatry practice, ethical and legal challenges often present hurdles in delivering care. Training in undergraduate and post graduate periods in tele-health may be essential now given the surge in tele-health interventions. Most studies report in session challenges such as frequent disconnections, poor audio-visual quality and it could limit mutual connection and understanding between the patient and therapist. This can be solved with preparation with dedicated internet connections with adequate bandwidth, quality hardware with adequate power back up, and basic training in online etiquette. Clinician comfort in delivering interventions can be navigated via

adequate training, having dedicated office space and fixed appointments (Naskar et al., 2017; Malhotra et al., 2013).

## **TELEPSYCHIATRY- IMPLICATION FOR PSYCHIATRIST'S STRESS**

The practice of telepsychiatry proposes many conveniences such as saving time and money by avoiding commuting to and fro to remote and rural areas. This, in theory, could provide more time for self-care, quality time with family, social outings and improve productivity and better work life balance. It may also reduce stress by decreasing the occupational hazard of exposure to agitated patients and violence by practicing telepsychiatry in setting such as prisons. However, the risk of social isolation and need for additional training may worsen stress among psychiatrists. Telepsychiatry may further contribute to a sedentary lifestyle. The need to check emails and work from home may blur the separation of work and home life and eventually contribute to burnout. The mode itself will demand a mental health professional to learn new skills and to adapt existing knowledge to suit these new skills on a technological platform in an ever evolving technological world. This itself may act as a stress for many mental health professionals. The transition from traditional mode to e-mode of health care is stressful for patients and mental health professionals (Vogt et al., 2019).

## **MANIPAL MODEL OF TELEPSYCHIATRY**

Department of Psychiatry at Kasturba Medical College at Manipal in Karnataka delivers telepsychiatry services since 2016 at four centres: Primary Healthcare Centre, Kandluru; Community Health Care Centre, Byndooru; Community Health Care Centre, Hebri and a private hospital in Basavakalyan.

Udupi is known for its beaches and belt of Western Ghats in addition to pilgrimage. The terrain varies from beaches to hills with some naxal affected areas. Certain areas are deprived of health care facilities due to various reasons. To address this issue Department of Psychiatry of Kasturba Medical College, Manipal had planned telepsychiatry services in both collaborative and direct to patient consultation models. Implementation of this Manipal Model of Telepsychiatry was in following manner.

**Collaborative care consultation model**

First, PHC was identified with the help of Psychiatrists in district, who helped us in locating the area which required specialist's care. The Primary Healthcare Centre (PHC) chosen was Kandlur PHC, in Kundapura taluka. Video conferencing applications Skype and Hangout (Google talk) were considered. It required two laptops and two webcams and internet connection. Manipal Academy of Higher Education responded positively and provided required laptops, webcams and logistics - vehicle for travel. Hospital internet connection has good enough speed for video-conferencing. At PHC, they offered to use their Internet service. Trial run was done in April 2016 and both Skype and Hangout chat services were found to be of optimal use for the venture. Subsequently services were initiated in 2 more centre in Udupi district: Hebri taluka Community Health Centre (CHC) in April 2017 and Byndooru Community Health Centre (CHC) in September 2017. Work pattern in these 3 centres: Designated fixed days in each month were decided in each centre, usually in first week of each month. One Psychiatry junior resident and One Psychiatric Social Work (PSW) trainee will go to these 3 centres. Resident and trainee will be organizing the camp, coordinating with the doctor at Government centre. The psychiatry resident and PSW trainee will interview patient in a designated interview room at the centre in front of a laptop (spoke) and this interview will be viewed and supervised in real time by consultant psychiatrist in Psychiatry Department at Kasturba hospital, Manipal (Hub). After the interview by resident/ PSW trainee, consultant psychiatrist will also interview patient for any clarifications then a diagnosis is established after discussion and medications will be prescribed by the psychiatry resident and medications will be dispensed by the pharmacy of Government hospital. Psychiatric Social Work trainees will carry out required psycho-social interventions. Any additional required medicines will be indented by PHC and will be made available free of cost for patients. Meanwhile, talks on mental health were delivered by PSW trainee to all patients in their waiting area in the particular centre. This is a collaborative care model.

**Direct to patient consultation model**

Another centre of telepsychiatry service is Basavakalyan in Bidar district, which is located 800km from Manipal. Different model, direct to patient model, is followed in this centre. Here, liaison with a private hospital was done and memorandum of understanding(MOU) was signed with Non-Governmental Organization (NGO), Nesara, for logistic issues. The site, being the native place of primary author, was visited by the primary author on monthly basis since January 2014 for delivering

mental health services, and it was converted to telepsychiatry direct to patient model since September 2016. Here, the NGO looked after the logistics and coordinated with the patients. Private hospital had paediatrician, who would assist in physical examination and any other needs. Patient would be sent to telepsychiatry cabin and first author would interview patients and prescription would be emailed to the private hospital and a print of same was given to the patient. Medications were dispensed by the pharmacy of the private hospital for free. These medications were provided by Chittasanjeevini Trust, Bengaluru.

Till December 2019, the number of patients seen in each centre were: 1912 in Basavakalyan, 1604 in Kandluru, 587 in Byndoor and 526 in Hebri.

Initial apprehension of using this for mental health care delivery disappeared after getting tuned to it. Patients were also comfortable in conversing with consultants in video chat. Consultant was able to follow full interview and clarify as and when need arose and suggested medications and non-pharmacological interventions. Regular usage provided newer insights and newer challenges in terms of implementation, which require modifications in strategies. Additional advantages were: training of junior residents in telepsychiatry, imparting skills to organize camps and working in liaison with public and private bodies, training of residents in delivering talks on mental health for common man, supervised training in interview skills.

Commonly seen disorders in these centres were: mood disorders, schizophrenia, epilepsy, anxiety disorders, somatoform disorders, substance use disorders and somatoform disorders. Stress related to stigma of illness, cost, travel, time, quality care, doctor-patients relationship, convenience emerged as the common themes in a qualitative study (unpublished data) done at these centres. Patients and family members expressed that, the above mentioned issues were areas of concern in traditional mode of care and telepsychiatry was able to address those concerns. Psychiatrists expressed stress related to satisfaction with mode of care as they felt face to face is always better. Network related issues, limited availability of medicines at Government centres, documentation process, rotation of junior residents emerged as sources of stress for both patients and psychiatrists.

Despite limitations, telepsychiatry mode was found useful not only to cater mental health needs of community but also in addressing stress related to illness and

resources required for the care. Meanwhile, the quality of healthcare and outcome of services was comparable with real time/face to face/in-person patient care.

### **Limitations And Future Directions**

Currently most evidence stems from studies done with a smaller sample size and cannot be generalized into a larger sample size to confirm the efficacy of the interventions for stress management. Current evidence lack long term follow up data and the cultural diversity across nations prevents extrapolation of evidence across settings. It would also help to study sustainability and effectiveness of the interventions in improving long term outcomes. The outcomes are also often incomparable due to the due to the heterogeneous nature of the interventions. There is a call for more extensive research in the area using stringent RCT designs, and clinical trials where possible, to ensure a high quality of data and to minimize the risk of bias. There is a need for establishing the cost-effectiveness of telepsychiatry for stress management through robust methodologies for the dissemination of its use (Malhotra et al., 2013).

Different models of telepsychiatry are adopted based on resources available and to suit needs of a particular centre or professional. This acted as hindrance to generalize the outcomes. Telemedicine operational guidelines and telepsychiatry practice guidelines released in India during COVID-19 pandemic have provided clear guidelines about what constitutes telepsychiatry, operational guidelines in lines with existing standards of care and in ethical and legal frameworks (MOHFW, 2020). With the advent of these, future decades will witness uniformity in studies and results which can be extrapolated to a larger population.

## **CONCLUSIONS**

The chapter draws attention to the fact that telepsychiatry has the potential to positively address stress in the context of physical and mental health issues. It has promise in improving assessment and management of stress, increasing access to mental health services, and overall promoting a healthier lifestyle. They have the potential to reduce the symptoms of stress, depression, and anxiety. In countries like India, where mental healthcare resources are falling short of the need and rapid evolution of usage of technology, internet and smartphones, coming years will witness a smart phone compliant population and unique challenges associated with it. By joining this tide of technological evolution, mental healthcare delivery can be made accessible to all. Considering the prevalence of mobile phones across the

world, these interventions could benefit participants globally. More research needs to be directed into the testing and validation of tele-health interventions to build a more evidence-based management approach.

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## **On Never Giving Up**

*Out in the cold, alone and blue  
Tired and beaten, on days not just a few  
I walk in the same pastures, the grass as sharp as knife  
My shoulders sagging down from the hassles of life  
It's night in the day when the heart cries out  
With ample woes to croon on about  
Not a hand to the left and none to the right  
But there is a twinkle in the gleam of moonlight  
Reaching out to my silhouette in the distant night  
I look to my shadow for strength with no one else in sight  
As my knees buckle and my ardour fails  
The boats of hope and strength have raised their sails*

***Supriya Dastidar***



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