WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 12, 586-610 Review Article ISSN 2278 – 4357

BIOPSYCHOSOCIAL PARADIGM OF SUICIDE AND ITS SCOPE OF MANAGEMENT: A REVIEW

Dr. Gargi Mondal*[1], Dr. Nirmalya Mukherjee[1] and Dr. Daya Ram[2]

[1]NIMHANS, Bangalore, India.

[2]CIP, Ranchi, India.

Article Received on
15 Oct. 2018,

Revised on 05 Nov. 2018,
Accepted on 25 Nov. 2018

DOI: 10.20959/wjpps201812-12820

***Corresponding Author**
Dr. Gargi Mondal
NIMHANS, Bangalore, India.

ABSTRACT

Suicide is one of the leading causes of death worldwide. From the scientific point of view, this complex problem of self-destructive behaviour involves biological, psychological and sociological perspectives. Classification and stratification of suicidal behaviour is highly important in identifying high risk groups and offering better rehabilitation to suicidal patients. This review explores the neurobiological, epigenetic and endophenotypic approaches of suicide. Gender difference in suicidal behaviour is an important area of research. An attempt has been made to identify peripheral biological predictors of suicide. Findings of gene expression studies occupy special importance in this review article. Finally, the latest developments in the management of suicidal behaviour have been summarised. Public health strategies to prevent suicide have also been mentioned.

KEYWORDS: Suicide is one of the leading prevent suicide have also been mentioned.

INTRODUCTION

The earliest account available regarding suicidal behaviour is found in De Maladies Mentales by Jean- Etienne Esquirol (1838), who said ‘‘all those who commit suicide are mentally ill”. In 1897, Emile Durkheim in his book Le Suicide said ‘‘suicide rates can be explained only by sociology”. Hollingshead and Redlich suggested that the diagnosis of psychopathology was, itself, influenced by social status. The stress-diathesis model implies that suicidal behavior is a result of interaction of traits (genetic and biological factors) and environment. In spite of the ambiguous definitions and various probable causes of suicide, the main concern is to prevent suicidal behaviour.

Classification of Suicidal Behaviours

Behaviours to harm self with or without the intention of death have never been defined or classified uniformly till date. So, researchers find it difficult to compare their study populations or results, and clinicians face trouble to apply the valuable research findings into their day to day practice while dealing with patients at risk for suicidal behaviours. According to Jobes et al. (1987) probably the only important cause of differences and error in suicide statistics is the virtual absence of any standardized classification criteria that people from all disciplines can follow to analyze behaviours meant to harm self (Silverman, 2011).

Suicidality

The term 'suicidality' includes

a) Cognitions- ideation, intent, motivation, and planning.
b) Behaviors-threats, gestures, rehearsals, and attempts.
c) Emotions-patients feeling suicidal. (Silverman, 2011).

It is imperative to define a suicide attempt as a previous attempt is the best indicator of such lethal acts which may even lead to death by suicide. With a uniform definition, people at most risk of an index suicide attempt and people engaged in such lethal activities can be identified and thus can be helped in a better way. Unfortunately, such a definition has not yet been standardized. (Silverman, 2011).

Deliberate Self-Harm (DSH) and Non-Suicidal Self-Injury (NSSI)

Kreitman termed the word 'parasuicide' to include all non-accidental hospital-treated self-poisoning and self-injurious behavior that ultimately did not result in death, irrespective of the intention of the act (Kreitman, 1977). The National Comorbidity Study (NCS) used this term to describe 'self-injury in which there is no intent to die, but instead an intent to give the appearance of a suicide attempt in order to communicate with others'. The DSH literature, as well as the suicide attempt literature, hardly distinguishes the populations by method (self-poisoning, cutting, etc.), location of the injury (wrists, arms, legs, head, etc.), physical location at the time of self-injury, time of day, day of week, etc. (Silverman, 2011).

Recent studies attempt to differentiate between DSH and suicide attempts in clinically important ways (Chapman & Dixon-Gordon, 2007). Suicide attempts are made in 'making others better off' (decreasing onerousness), while causes for DSH include 'anger expression' and 'distraction'. People engaging in DSH report that the act relieves inexorable stress and

restlessness; transiently decreases sadness, depression, and shame; or as a way of self punishment, relieves anger directed inward, self-blame and self-loathing for perceived social transgressions (Chapman and Dixon-Gordon, 2007). It has been reported that relief was the main motto of DSH, whereas feeling oppressive was the most common precedent of a suicide attempt. Yet, few individuals reported that their predominant emotional experience following DSH was mostly sadness. The two acts may be differentiated by the presence or absence of the critical factor of the intent to die. However, it is important to note that multiple motives often underlie both suicide attempts and DSH (Silverman, 2011).

Determining intent to die

The presence or absence of intent to die is a key factor in differentiating non-suicidal from suicidal self-harm behaviours (Silverman et al., 2011). Many patients who harm himself, when asked by clinicians at the time of the injury, will deny that they had an intent to die, despite the evidence to the contrary (e.g., high lethality of the act, prior history of near lethal suicide attempts, corroborating information from family, friends, or support network). Difficulties in diagnosis can arise when the assessment of the intent to die is denied by the patient yet some ambivalence is present. (Silverman, 2011). Suicidal behaviour can thus be broadly be grouped into two groups—a) Failed suicide- had intent to die but survived the attempt. b) Deliberate self harm—did not have the intent (Sarkar et al., 2006).

Few accepted classifications of Suicidal Behaviours

Beck et al., classification of suicidal behaviours (1973): This system stands on three factors: suicidal ideas; suicide attempts; and completed suicide. Each of these three types is further specified by: (a) certainty (0%–100%); (b) lethality (zero, low, medium, or high); (c) intent to die (zero, low, medium, or high); (d) mitigating circumstances (zero, low, medium, or high); and (e) method (list actual method used). (Silverman, 2011).

Columbia University suicidality classification: The 'Columbia Suicidality Severity Rating Scale' (C-SSRS) measures the degree of suicidal ideation and the level of lethality. Suicidal ideation is measured on a 1–5 point scale (from 'wish to die', 'active suicidal ideation', 'method', 'intent' to'plan'). Lethality is measured on a 0–4 scale with the level of severity defined as the frequency, duration, controllability, deterrents, and reasons for ideation. (Silverman, 2011).

Thus, an ideal goal should be to develop a classification system for suicidal behaviours based on degree of intent, lethality of method used, likelihood of rescue, degree of planning (impulsivity), and presence and status of psychiatric or medical illness. Scales or ranking systems can be developed to measure these elements. (Silverman, 2011). Though the diagnosis of 'suicidal behaviour' may have an ignominious effect, it will add a modest amount to the clinical assessment of current suicide risk. Such a category may help with research efforts to better detect and treat acute suicide risk. (Fawcett, 2012).

Can Risk of Suicidal Behavior Be Stratified?

Acute Suicide Risk

High Acute

a) Suicidal ideation with the intent to die.

b) Inability to maintain safety independent of external support or help.

They require close observation preferably in a secure psychiatric unit.

Intermediate Acute Risk

a) Perceived ability to maintain safety independent of external support or help.

b) Lack of intent may be present.

Psychiatric hospitalization should be considered for this group.

Low

a) Absence of current suicidal intent, a suicidal plan, any preparatory behaviour.

b) May have suicidal ideation.

Chronic Suicide Risk

High Chronic

A variety of risk factors are typically associated like chronic major mental illness, h/o prior suicide attempt, chronic suicidal ideation etc.

Routine mental health follow up, a safety plan, routine screening, restriction of means, development of coping skills are necessary.

Intermediate Chronic

Same as high chronic risk. Balance of protective factors, coping skills and psychosocial stability is present.

Low Chronic

Persons with little or no mental health or substance abuse problems to significant mental illness with a relative abundance of coping strengths and resources (Wortzel, 2014).

What is the Relation Between Distal and Proximal Risk Factors?

Individuals presenting the suicide diathesis may present a suicidal crisis when facing a difficult life event which would act as a proximal risk factor. The relationship between early-life adversity and suicide, as well as the effects of the neurobiological and trait-phenotype mediators, are moderated by several important factors such as gender, age, marital status, occupation, education, family structure, urban vs. rural residence, cultural context, spirituality and sets of beliefs about life and death. Specificity for suicidal behaviour may be determined by a combination of the distal risk factors. Specificity may be associated with the onset of proximal risk factors, such as depression and suicidal ideation. A better understanding of early neurobiological correlates of suicide risk may reduce the mortality and societal burdens associated with this complex neuropsychiatric phenotype. (Turecki et al., 2012).

Epigenetic Effect of Social Experiences: Juvenile Versus Adults

Although social modulation of brain and behaviour has been primarily explored in response to early social experiences, and in particular, mother-infant interactions, there continues to be plasticity in response to social experiences occurring during juvenile development and also in adulthood.

Social isolation during the post weaning period has generally been found to increase anxiety-like responses, though this may not involve the same neuroendocrine pathways targeted by earlier social experiences. In rodents, post weaning social isolation has been associated with decreased expression of several 5-HT receptor subtypes in the prefrontal cortex, hypothalamus, and midbrain; latent elevations in DA levels in the Nac (Nucleus Accumbens); reduced GABAA/CBZ receptor binding; decreased neuronal plasticity associated with glutamatergic hypofunction; and sex-specific effects on the numbers of (oxytocin)OT-positive neurons in the PVN. This cascade of neuroendocrine changes is associated with a phenotype referred to as an “isolation syndrome,” which can be attenuated by treatment with antidepressants. Juvenile environmental enrichment (typically involving both physical and social environmental complexity) in rodents attenuates the HPA response to stress with a concomitant decrease in basal corticosterone levels, and there is evidence for enrichment induced elevations in hippocampal NGFI-A (Nerve Growth Factor-A) and GR

(Glucocorticoid Receptor) (Olsson et al., 1994). In addition, social enrichment during juvenile development is associated with increased levels of the DAT, increased GAD enzyme activity and extracellular GABA concentrations within the hippocampus, increased AMPA receptor expression in the hippocampus, and elevated OTR binding in a number of forebrain and hypothalamic areas including the central nucleus of the amygdala.. Findings have suggested the role of epigenetic mechanisms in shifting gene expression and behaviour in this later stage of development (Champagne et al., 2011).

In adulthood, even a single social defeat is associated with prolonged alterations to the HPA stress response and changes to the expression of CRH receptors. Social defeat results in transient changes in GABA receptor levels in cortex, cerebellum, and hypothalamus; increases in NMDA and decreases in AMPA receptor binding in the hippocampus; and increases in expression of AVP mRNA in the PVN.

Exploration of the epigenetic pathways linking the experience of social defeat to the behavioural phenotype that emerges in response to this adult social stressor has focused primarily on BDNF, which serves as a trophic factor that is a common downstream mediator of the effects of the multiple neurotransmitter and neuropeptide systems. BDNF gene expression is significantly decreased in the hippocampus of socially defeated male mice and this effect appears to be mediated by specific decreases in the BDNF III and IV transcripts. Chromatin immunoprecipitation (ChIP) analysis indicates increased histone H3-K27 dimethylation at the BDNF III and IV promoters among socially defeated males, which may account for the reduced BDNF expression. Histone deacetylase (HDAC5) mRNA levels are also found to be decreased in socially defeated males and HDAC5 appears to be important in mediating the effects of antidepressant treatment in males exposed to chronic social stress (Renthal et al. 2007). The differential levels of histone H3-K27 dimethylation are also found across the genome within the NAc, both in response to chronic social defeat and prolonged adult social isolation (Wilkinson et al., 2009). Studies have shown that there is plasticity beyond the postnatal period, and that epigenetic mechanisms are responsive to juvenile and adult social experiences, with dynamic histone modifications more evident in response to the later life experiences (Champagne et al., 2011).

Are Adverse Situations Always Associated with Negative Outcome?

Not all individuals exposed to stress, will become vulnerable in future stress, rather majority remains stable through various adverse life situations. Human and animal studies consistently

show that stressful experiences can cause "steeling" effects, that is, strengthening social-emotional and neuroendocrine resistance to subsequent stressors. Studies have revealed that controllable stresses have some sort of "immunizing" effect on later stresses. Successful physiological and/or psychological coping following a severely adverse condition may strengthen an individual, thus making him resilient (Rutter, 1987). Different Neurobiological as well as genetic factors have been studied with respect to a resilient response to stress.

Neurobiology

- **Hypothalamo-Pituitary-Adrenal Axis**

Ability to limit stress induced increase in corticotrophin releasing hormone (CRH) and cortisol by a negative feedback mechanism along with an optimal balance of glucocorticoid and mineralocorticoid receptor function have been found to be associated with resilience. Higher dehydroepiandosterone (DHEA) to cortisol ratio is also probably involved in the mechanism.

- **Monoaminergic and Catecholamine System**

There are various systems involved. Inhibited responsiveness of the noradrenergic system in locus coeruleus is seen in resilience. Role of dopeminergic system is unclear. Serotonergic system has both anxiolytic and anxiogenic effects in response to stress depending on the region of brain and the receptor involved.

- **Others**

Neuropeptide Y has been implicated in balancing the anxiogenic effects of CRH in the amygdala, hypothalamus, hippocampus and locus coeruleus thus contributing to resilience. Where as BDNF has not to be shown any increase in Nucleus accumbens.

Genetic Influence

1. Hpa Axis Related Genes: CRH type 1 receptor gene (CRHR1) moderate influence of childhood trauma with few alleles (rs7209436 and rs242940) exerting a protective effect. Four single nucleotide polymorphisms (SNP) of the gene FKBP5 is also important.

2. Serotonin Transporter

Though study results are ambiguous, limited studies show association of long allele of 5-HTTLPR and emotional resilience in college students.

3. Catechol-O-Methyl Transferase (COMT)

Individuals with the low-functioning Met158 allele of the COMT gene and thus having higher circulating levels of dopamine and noradrenaline tend to have lower resilience to negative mood states, and increased reactivity to unpleasant stimuli.

4. NPY: The level of *NPY* mRNA expression showed an inverse correlation with trait anxiety, and a direct correlation with levels of stress-induced endogenous opioid release.

Gene-Gene and Gene-Environment Interactions

Monoamine oxidase A (*MAOA*)-*COMT* interaction affects the endocrine responses to a psychological challenging task. *5-HTTLPR-COMT*-stressful life events interaction affects the risk for depression, and a *COMT-5-HTTLPR* interaction affects limbic reactivity to unpleasant stimuli in healthy subjects. Social support seems to balance the effects of the short allele of *5-HTTLPR*, and the *5-HTTLPR* and *BDNF* Val66Met genotypes interact with stressful life events to predict risk for depression (Feder et al., 2009).

Endophenotypic Approach: A Link Between Genetic and Behavioral Approach

Endophenotype is a genetic epidemiology term which is used to parse behavioural symptoms into more stable phenotypes with a clear genetic connection. Gottesman and Gould established five criteria that should be fulfilled by the endophenotypes in genetic psychiatry:

1. The endophenotype is associated with the disease in the general population.
2. The endophenotype is inheritable
3. The endophenotype is a marker of stable trait, independent of the disease status
4. the endophenotype and the disease co-segregate in the family
5. the endophenotype is manifested in unaffected relatives with greater frequency than in the general population. (Gottesman II et al., 2003.)

The various endophenotypes are

a) Impulsivity—aggression. The most reproduced associations between suicide and personality measures are with indicators of aggression and impulsivity, which meet most, if not all, stringent endophenotype criteria.

b) Disadvantageous decision making- A significantly higher tendency toward disadvantageous choices was found in patients with a history of suicidal behavior compared with patients without any such history and to healthy controls.

c) Altered skin conductance- An association has been found between a stimulus-elicited electrodermal response (hyporeactivity), as measured by skin conductivity, and suicidal behavior in several studies. Moreover, electrodermal activity during decision making seems to implicate key brain regions associated with SB, such as the ventral and medial prefrontal cortices (Courtet P, et al. 2011, Treviño et al., 2011).

d) Neuroimaging- At the neuroanatomical level, postmortem studies have implicated involvement of the prefrontal cortex, particularly the most ventral regions including the orbitofrontal cortex. Cannon et al. found increased binding of the serotonin transporter in the anterior cingulate gyrus of bipolar patients with a history of suicide attempts compared with those without a past history of attempts. Leyton et al. reported reduced levels of a [11C] methyl-Ltryptophan in the ventral and lateral prefrontal cortex of high-lethality suicide attempters compared with healthy controls. Positron emission tomography imaging has shown that there is reduced activation of the medial prefrontal cortex in high versus low lethality suicide attempters (Courtet et al., 2011).

The endophenotypic approach may provide trait markers of susceptibility to disease, models of the disease process, improvements in classification and diagnosis, elucidation of new therapeutic targets, and improvements in the development of animal disease models. However, the endophenotype approach may not be most appropriate to discover new genetic polymorphisms related to disease (Courtet et al., 2011).

Intermediate Phenotypes

Intermediate phenotypes emerged recently to be a precious tool in the search for the genetic underpinning of complex traits and diseases. Intermediates can be regarded as syntheses of subsets of proximal risk factors, both environmental and genetic (Rujescu et al., 2012).

Aggression

A link between aggression and suicidal behavior has been shown in schizophrenia, borderline personality disorder, substance use disorders, and nonclinical samples (Turecki, 2008; Rujescu D, et al. 2012).

Impulsivity: Aggressive behaviors have been shown to correlate with impulsivity, suggesting that an impulsive– aggressive dimension may predispose to suicidality (McGirr & Turecki, 2007; Rujescu D et al., 2012).

Anger

Trait anger has been associated with a previous history of attempted suicide. In adolescent suicide attempters, high levels of anger expression predicted self-mutilative behavior and a self-reported wish to die. In older suicide attempters, higher anger/hostility correlated with a greater number of attempts, while lower levels of anger predicted higher intent to die and higher lethality of methods. Furthermore, the association between anger and suicidality has been demonstrated in depression, eating disorders, and alcohol use disorders. (Painuly et al., 2007; Kirkcaldy et al., 2006; Rujescu D et al, 2012).

Temperament

Studies report elevation in the "Novelty Seeking" and "Harm Avoidance" and decrease in the character dimensions of "Self Directedness" and "Coperativeness" in suicide attempters compared to non-suicidal controls. Temperament dimensions associated with self-aggression were high harm avoidance, high impulsivity, and low self-directedness. Additionally, impulsivity and harm avoidance have emerged as temperament dimensions independently associated with self-aggressive tendencies in personality (Calati et al., 2008; Rujescu et al., 2012).

Neuroticism

Neuroticism, a personality trait, reflects a tendency toward negative mood states and has been included in most theories of personality since its introduction. Studies have consistently demonstrated associations between an individual's level of neuroticism and likelihood of having symptoms or syndromes of suicidal behavior, depression, or anxiety (Brandes & Bienvenu, 2006; Ormel et al., 2004; Rujescu et al., 2012).

Biology of Suicidal Behavior in Different Age Groups

Paediatric Age Group

Hypothalamic-Pituitary-Adrenal Axis

Some studies show no difference of results between suicidal and non-suicidal depressed children on the Dexamethasone Suppression Test. Other studies found that although there was no association between suicidal behavior and DST nonsuppression in prepubertal children, the patients with persistent suicidal behavior had significantly higher pre-dexamethasone 4 p.m. cortisol levels (Zalsman, 2012).

Growth Hormone

Kutcher et al. 1991 reported increased nocturnal secretion of growth hormone in depressed children, the reason may be that muscarinic hypersensitivity as a consequence of serotonin deficit may lead to excessive somatostatin inhibition and increased growth hormone secretion (Zalsman, 2012).

Neuroendocrine Challenge Studies

Studies suggest that suicidal behavior in youth is associated with a different pattern of serotonergic abnormality compared with adults, a pattern that may include greater 5-HT or 5-HT receptor responsiveness (the serotonin affecting prolactin release) (Zalsman, 2012).

Platelet Studies

Some authors found inverse relationship between H-imipramine binding and presence of suicidal behavior while others found no difference between adolescents with conduct disorder who attempted suicide and non suicidal controls with conduct disorder. However, the suicidal group showed significant seasonal variations of H-imipramine binding with the lowest amount in late winter/early spring (Zalsman, 2012).

Post Mortem Studies

It has been found that 5-HT receptor protein and mRNA levels were higher in the pyramidal cells of layer V of prefrontal cortex and hippocampus but not in the nucleus accumbens of adolescent suicide victims as evident in the adult population. (Zalsman, 2012).

Sleep Related Studies

Studies show ambiguous relationship between sleep abnormalities and suicidal behaviour. Few of them found no difference between suicidal and non-suicidal depressed adolescents, while others show higher sleep latency in suicidal adolescents and possibly shorter REM latency compared with other depressive adolescents as well as significantly higher REM density among suicidal depressives. The relationship between sleep and the serotonin system should be thus further studied. (Zalsman, 2012).

Teenage Suicide

It was observed that the mRNA levels of the different G proteins were significantly altered in the prefrontal cortex of adult suicide victims compared with adult control subjects. In contrary, no significant difference in mRNA levels of any of the G protein subunits was

found in the teenage group. This suggests differential abnormalities of G-protein subunits between the adult and the teenage suicide victims (Pandey & Dwivedi, 2012). Teenage suicide is associated with decreased protein kinase C binding sites in the prefrontal cortex suggesting some preliminary evidence of abnormalities of protein kinase C in teenage suicide victims (Pandey & Dwivedi, 2012). cAMP response element binding protein (CREB) expression was found to be significantly decreased in the hippocampus of adults but not of teenage suicide victims, though there was no such difference observed in the prefrontal cortex (Pandey & Dwivedi, 2012). BDNF expression was found to be significantly decreased in the hippocampus of adult suicide victims compared to the teenage group. No change in protein and mRNA expression of TrkB was evident in both teenage and adult suicides (Pandey & Dwivedi, 2012).

Suicide in the Elderly Population

The neuroendocrine and neurocognitive correlates of suicidality in the elderly revealed hypothalamo-pituitary-adrenal axis dysregulation to be associated with increased suicide risk. Cognitive impairment like impairment in executive function, memory, and attention was associated with suicidal ideation. The cognitive impairments have also been linked to poor decision making seen in suicidality.

What are the Causes of the Gender Difference Observed in Suicidal Behavior?

It has been observed in diverse population that women outnumber men with respect to attempted suicide, but men are more likely to complete a suicide than women are. Evidences accumulated from multiple studies indicate that "ID may disrupt the functional integrity of inhibitory neurotransmitters and thereby contribute to poor impulse control and conduct disorder" in genetically vulnerable individuals.

Biological Basis

X Chromosome: One study found differential expression of genetic factors to be related to the gender moderation of suicidal risk. It showed two regions on the X chromosome, one on the long arm demarcated by DXS8051 and DXS8102 and the other on the short arm demarcated by DXS1001 and DXS8106 were responsible for this. Moreover, six genes – Rho-GTPase activating protein activating 6, Glycoprotein M6B, spermidine/spermine N(1) acetyltransferase 1, ribosomal protein S6 kinase, THO complex 2 and adapter related protein complex 1 sigma 2 subunit were found to be differentially expressed in Brodmann areas 8/9, 11, 44, 46 (Fiori et al., 2011).

Neuroendocrine Response to Stress

Multiple studies together suggest greater HPA axis dysregulation in women than men with stress-related psychiatric disorders. Sex difference in CRF sensitivity probably mediated by the pubertal ovarian hormone surge has also been suggested by multiple studies.

Sex Difference in Negative Valence

Several functional neuroimaging studies have shown sex differences in the magnitude of corticolimbic responses (corticolimbic system being comprised of the amygdala, prefrontal cortex and hippocampus) to emotional stimuli. Moreover, women have greater hippocampal activation than men when encoding emotional words (Bellace et al., 2013). Some studies show negatively valenced words activated the left perirhinal cortex and hippocampus in women, but the right supramarginal gyrus in men. Still other studies reveal that in some cases, emotional stimuli activate the same structure in men and women, but the degree of this activation is distinguished by lateralization. A recent paper found that depressed men have abnormalities in prefrontal-striatal circuits, but women have abnormalities in prefrontal-limbic circuits, which, as noted, processes negative emotions (Kong et al., 2013). Reviewed results indicate that the hippocampus, amygdala, and cortex contain sexually differentiated dendritic morphology and/or spine density which probably result from sex differences in intracellular signaling events that induce cytoskeletal remodeling.

Role of Iron Deficiency

Poor iron status alters myelination, neurotransmitter metabolism and function, cellular and oxidative processes, and thyroid hormone metabolism. Decreased brain iron stores may impair the serotonergic system, the main pathway involved in suicidal behavior. Brain does not produce adequate dopamine when an iron deficiency is present, this may also contribute to the gender difference observed.

Environmental Basis

It is possible that there is a variation in the level to which dissonance pass on directly on boys and girls. It was noted that parents wrangled more in front of boys than girls. Secondly, after a family separation, sons are more likely than daughters to be placed in some form of institutionalized care which increases the possibility of psychopathogical risk. Third, boys are more likely than girls to respond with disruptive oppositional conduct. Fourthly, hostility in boys is more likely to be met with either penal or withdrawal consequences from adults and negative responses from peers. Stevenson- Hinde and Hinde found that whereas shyness in

boys is associated with negative interactions with others, in girls it is associated with positive personal interchanges. Dunn and Kendrick's data suggest that mothers are both more punitive with sons than daughters and also more consistently so over time, an outcome likely to lead to intensifying negative behaviour (Rutter, 1987).

Are There any Peripheral Biological Predictors of Suicidal Behavior in Major Depression?

To identify a promising biological predictor or marker for suicidal behaviour has been quite difficult because most suicide risk factors have a low specificity, and the rate of suicide is relatively low in general population. A coupling of CSF 5-HIAA and DST non-suppression and a coupling of serum cholesterol and DST non-suppression have shown promising results in this regard. Specifically, it is indicated that CSF 5-HIAA and DST non suppression are independent biomarkers, and CSF 5-HIAA may reflect short-term suicide risk, while dysregulation of the HPA axis may be a more long-term predictor of suicidal behaviour. These findings appear to be an even more prominent predictor among individuals with major depression or with a previous history of attempted suicide. It was suggested that low CSF 5-HIAA and serotonin dysfunction might be a marker of the diathesis, and DST non suppression and HPA axis hyperactivity might serve as a marker of the acute stress response. Platelet 5HT receptors and CSF 5HIAA are also beneficial biomarkers for suicidal behavior. Components of HPA axis and cytokines are to be delved into further. Cholesterol and BDNF levels in blood serum or plasma may be lowered along with impaired brain plasticity among individuals with suicidal behavior and ideas. Lower docosahexaenoic acid percentage of total plasma polyunsaturated fatty acids and a high omega-6/omega-3 ratio predicted suicide attempt. Eicosapentaenoic acid was found to be lowered in red blood cells of suicide attempters compared to controls. As suicidal behavior is a complex phenomenon, a multidimensional approach, including a combination of biological factors and psychosocial factors might be helpful in predicting suicidal behaviour and identifing suicidal patients. A useful biomarker should not only reflect the suicidal behaviour, but should also be measured in a noninvasive manner. (Jokinen et al., 2009; Lee B-H, et al. 2011).

Future Avenues for Gene Expression Studies: In spite of the fact that understanding of the neurobiology of suicide has greatly increased within the last few decades, we are far from implementing the knowledge in developing an integrated picture of how specific biological and neurochemical alterations interact to confer risk for suicidal behaviours and how these

findings can be used to treat these behaviours. Focus of majority of studies was directed on genes and proteins of interest, and while these studies continue to be important, they are not sufficient to address these issues. Microarrays have played an essential role in highlighting new molecular pathways involved in suicidal behaviour, yet cannot explain either the origin of these alterations or the nature of their short- and long-term effects on brain function. However, various advances in different fields like clinical, genetics, epigenetics, ecogenetics, proteomic, or metabolic studies, and collaboration of these fields, a more comprehensive view of these processes will be possible (Fiori et al., 2012).

1. Gene Function

Although it is clear that specific alterations in gene expression underlie the suicide process, the functional impact of these alterations remains largely unknown and represents an essential step in understanding the pathological effects of gene expression differences (Fiori et al. 2012).

Several methods are now available to study these effects.

- Microarray studies designed to measure the expression of the 3′ end of mRNA.
- Use of exon arrays to identify genes showing specific splicing differences.
- Advances in sequencing methods to directly sequence and quantify the transcriptome.
- RNA-Sequencing (Fiori et al. 2012).

In the future, integrating mRNA expression with protein expression data will allow for a better understanding of the functional effects of alterations in gene expression, and how they may ultimately lead to suicide. Neuroimaging techniques are to be further developed. Protocols for laser capture micro dissection have been optimized for postmortem brain tissues (Pietersen et al., 2009), which will be invaluable in better characterizing the specific roles played by neurons and glia in suicide (Fiori et al. 2012).

2. Gene Regulation

Integration of gene expression data with that obtained from platforms assessing single nucleotide polymorphisms (SNPs) across the genome, is needed to obtain the essential information regarding the regulation of gene expression. Genetic regions, associated with gene expression differences, may represent specific functional genetic variants. These may also be due to larger chromosomal alterations, known as copy number variations (CNV), which have been linked with psychiatric disorders including bipolar disorder, schizophrenia,

and autism. Genetic studies at a larger scale are now possible using comparative hybridization arrays, large scale genome based deep sequencing, and chromatin immune precipitation based methods. (Cook & Scherer, 2008; Chen et al., 2009; Fiori et al., 2012).

Epigenetic modifications are also key regulators of gene expression. It is believed that they may mediate the interaction between the genome and the environment. For the epigenetic modifications micro RNAs are important mechanisms as well. Assessment of each of these epigenetic mechanisms using high-throughput methods, in conjunction with gene expression microarrays, will allow the methodical analysis of epigenetic effects that may be concerned in suicide risk. In addition, as epigenetic markings are potentially reversible, this is an exciting area of exploration that creates the opportunity for therapeutic intervention. (Chen et al., 2009; Fiori et al. 2012).

3. Methodological and Phenotypic Considerations

With most of the genetic findings of suicidal behaviour being nominal or mixed, it has become apparent that there are numerous issues that need to be resolved as we move toward more comprehensive and large-scale genome-wide studies. (Roy, 2012).

1. Gene–Gene Interactions

Perroud et al. (2009) found a significant interaction between BDNF and NTRK2 polymorphisms in suicidal ideation. With large datasets from genome wide association and gene expression microarray studies, pathway analysis using ingenuity pathway analysis could be a viable option for more comprehensive analysis of gene pathways in suicidal behaviour (Roy A, 2012).

2. Scope of Gene Environment Interaction Studies

- None of the studies showed any direct effect of genotype on suicidality but did show positive GXE results which support the view that "in psychiatric genetics, ignoring nurture handicaps the field's capacity to make new discoveries about nature," that is, suicidal behavior. Thus, it is imperative for there to be more GXE studies of suicidal behavior.

- Most of the GXE studies of suicidal behavior have studied the interaction of genes with the early life event of childhood trauma. This pertains special mention as Rutter (2010) concluded that if "GXE may bring about biological changes through epigenetic mechanisms operating mostly in early life … it would seem to favor maltreatment rather than current life

events as the key environmental hazard." So future GXE studies of suicidal behavior should consider to include a measure of childhood trauma.

3. Other Considerations

Sample enrollment practices and statistical analyses must be accustomed in order to identify gender-specific factors. Additionally, there is a need for increased sample sizes as well as the availability of well characterized and appropriately selected control groups in order to enable the identification of phenotype specific gene expression changes, a particularly important challenge in neurobiological studies of suicide. Finally, developing a more comprehensive view of the means by which psycho-pharmacological agents affect gene expression is an important step in understanding the mechanisms by which they exert their therapeutic effects, which will greatly assist in the development of better treatments directed toward suicidal behaviors (Fiori et al., 2012).

Therapeutic Targets

Studies comparing the effects of different antidepressants on suicidal outcomes provide knowledge about the most salient neurobiological actions that affect suicidal ideation and behavior. Few studies show that drugs acting primarily on the serotonergic system compared to drugs acting on the noradrenergic system are more effective in improving suicidal ideation. One study found the noradrenergic drug to be more efficacious. Different study durations, patient types, and treatment protocols make it difficult to draw concrete conclusions but it seems to indicate that the serotonergic system is one of the key targets for pharmacotherapeutic approaches to suicide prevention (Mann & Currier, 2012).

Pharmacological Management

Lithium

One of the mechanisms proposed for lithium's antidepressant effect is that it enhances serotonin neurotransmission. Meta-analyses and observational studies show that lithium decreaseses the risk of suicidal behavior by increasing serotonin release as well as prolactin following the administration of l-tryptophan. Evidences show that aggression and impulsivity, both associated with suicidal behavior, and both of which are influenced by impaired serotonergic function, are decreased by lithium. Lithium also augments antidepressant effect which may reduce suicide risk (Mann & Currier, 2012).

Clozapine

Suicidal behavior and aggression has been associated with higher serotonin 2A receptor binding. One mechanism through which clozapine exerts its anti-suicidal effect is by blocking of this receptor. Other atypical antipsychotics blocking the 5-HT receptor are being studied in terms of suicide risk (Mann & Currier, 2012).

Endocannabinoids

Relation of the endocannabinoids with suicidal behaviour has been established by the activation of multiple signalling pathways by the CB1 receptor and/or existence of subtypes of CB or CB1 receptors. Future studies should elucidate whether the dysfunction of the cannabinoid system is directly associated with the pathophysiology of depression and suicide or if they are part of neuroadaptative changes in response to alteration in some other neuronal substrates. Finally, treatment of alcohol addiction and stress-related disorders can eventually reduce the rate of suicide (Vinod, 2012).

Other Agents

Both positive and negative associations of antiepileptic drugs have been found with suicidal ideations. They act mostly by enhancing GABAergic inhibitory function in the cortex and thus questioning the impact of GABA on suicide risk as an area of further research. PUFA profile can predict suicide attempt risk and probably omega-3 supplements may help in reducing risk. Ketamine, an NMDA antagonist, is a very rapidly acting antidepressant which has been reported to have a profound therapeutic benefit for suicidal ideation. It is an AMPA receptor antagonist and raises GABA levels and perhaps those properties contribute to its rapid and profound reduction in suicidal ideation. Other new agents targeting the corticotrophin-releasing factor 1 receptor, neuropeptide Y, vasopressin V1b, Nmethyl-daspartate, nicotinic acetylcholine, dopamine D1, glucocorticoid system, δ-opioid, cannabinoid and cytokine receptors, γ-amino butyric acid (GABA), intracellular messenger systems, transcription, and neuroprotective and neurogenic factors are being studied. (Mann & Currier, 2012).

Non Pharmacological Management

Psychotherapies

Cognitive Behavioural Therapy is based upon the hypothesis that people continue to learn throughout their lives. CBT helps patients to learn and adopt new knowledge and skills, which will enable them to observe and change their own thoughts, behaviour, and emotional

states. Research showed that neurobiological basis of CBT includes synaptogenesis, neurogenesis (Bjorklund & Lindwall, 2000), and programmed cell death. CBT brings the change in human brain through neuroplasticity, that is, creation of interconnections between neurons based on their simultaneous firing over a period of time as rightly elaborated by "neurons that fire together, wire together"/"neurons that fire apart, wire apart". It has been established that synaptic plasticity is the molecular basis of learning and memory and that learning accompanied by the development of new neuronal connections also leads to the development of new neurons (Gould et al., 1999).

The Research Domain Criteria Project applies neurobiological knowledge in developing psychotherapeutic approaches. 'ENGAGE' is an example of a streamlined therapy. It consists of 'reward exposure' but the clinician searches for 'negativity bias', 'apathy' and 'emotional dysregulation', and adds strategies targeting these domains when required. The final outcome is a structured, stepwise procedure using neurobiological constructs as targets and as a guide to personalized treatment (Alexopoulos & Arean, 2014).

Electroconvulsive Therapy

- **Changes in Brain Structure**

ECT may affect the structure of the hippocampus, alter anterior cingulate/prefrontal cortex rCBF (cerebral blood flow) or rCMR (cerebral metabolic rate) and normalisation of reduced anterior cingulate theta wave activity.

- **Changes in Neurotransmitters**

A human positron emission tomography (PET) study reported decreased anterior cingulate dopamine-D2 receptor binding after ECT. ECS may restore GABa-ergic inhibition and modulate glutamate receptor expression or function. ECT increases brain and cerebrospinal neuropeptide Y concentrations. One PET study using the radioligand [carbonyl-11C]WAY100635 suggests a global reduction of the postsynaptic 5-HT1A receptor binding after ECT in cortical and subcortical regions except the occipital cortex and the cerebellum(Lanzenberger et al., 2013).

- **Endocrine Changes**

ECT normalises HPA axis dysfunction, including restoring dexamethasone suppression of cortisol. It also brings surges in plasma catecholamine concentrations.

- **Genetic Changes**

ECT enhances neurogeesis in the hippocampus, the subventricular zone (SVZ) and in the rostro-medial striatum, creating specific, small-size calretinin-positive interneurons. ECT also influences angiogenesis, gliogenesis, glial cell activation and recruitment of blood-derived macrophages.

Repetitive Transcranial Magnetic Stimulation (rTMS)

It acts through alteration of synaptic connections (neuro plasticity), resulting in long term potentiation or depression, depending upon the frequency of field used. High frequency rTMS(>1 Hz) leads to activation of cortex by potentiation, whereas low frequency rTMS (<1 or 1 Hz) leads to depression of cortex by depression. In major depressive disorder, either there is hypo-activation of left dorso-lateral prefrontal cortex or hyper activation of right DLPFC. Accordingly high frequency rTMS over left or low frequency rTMS over right DLPFC are effective in treating depression.

Future Scope

In light of the interpersonal theory of suicide, it has been found that anger is associated with suicidal ideation and behaviour through discerned onerousness, baffled belongingness and greater acquired capability for suicide via experiences with painful and provocative events. It may be thus concluded that controlling the problematic anger may benefit the patient at risk for suicide (Hawkins et al., 2014).

Public Health Strategy

In 1998, WHO Cabinet launched Suicide Prevention (SUPRE) programme whose motto was "reducing mortality, morbidity and other consequences of suicidal behaviors," by.

1. Limiting the availability of aids to suicide (e.g., toxic substances, car exhausts, gun availability, physical barriers).
2. Proper care of the mentally ill.
3. Good media reporting about suicide.

Psychobiotics

Dinan (2013) defined "psychobiotic as a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness". Serotonin, the mood elevating neurotransmitter is produced by *Candida, Streptococcus, Escherichia,* and *Enterococcus.* Oral intake of *Bifidobacterium* infantis (B. *infantis*) increases levels of the

serotonin precursor tryptophan. *Escherichia, Bacillus* and *Saccharomyces* produce norepinephrine whereas *Baccilus* and *Serratia* produce dopamine. The products of the psychobiotics function through the brain-gut axis, probably via the neuroendocrine system, spinal cord and vagus nerve. Evidence is accumulating that they can resolve depressive symptoms by their anti-inflammatory actions and by reducing hypothalamic-pituitary-adrenal axis activity. Further studies are awaited (Dinan et al., 2013).

Pharmacogenomics

Genetic factors play an important role in response to drug treatment and side effect profile of drugs. Genetic polymorphisms affect the pharmacokinetics and pharmacodynamics of the drug and thus influence the prognosis of the disease. Identification of genetic variants by genome wide studies may help to offer a personalized treatment for a better benefit (Moller & Rujescu, 2010).

CONCLUSION

As clinical predictors of suicide risk have poor effectiveness, genomics and brain imaging are the most promising new directions for detection of patients at high risk for suicide. Imaging–genetic approaches, might serve to identify the association between circuitry-related changes and gene function and suicidal behaviour. Genomic markers and neuroimaging might identify patients at high risk of suicide and help to identify personalised interventions for the prevention of suicidal behaviour.

REFERENCES

1. Alexopoulos GS, Arean P. A model for streamlining psychotherapy in the RDoC era: the example of ‘Engage’. Mol Psychiatr, 2014; 19: 14-19.
2. Bellace M, Williams JM, Mohamed F, Faro SH. An FMRI study of the activation of the hippocampus by emotional memory. Int. J. Neurosci, 2013; 123: 121-127.
3. Bjorklund A, Lindvall O. Self-repair in the brain. Nature, 2000; 405: 892-895.
4. Brandes M, Bienvenu OJ. Personality and anxiety disorders. Curr Psychiatry Rep., 2006; 8: 263-269.
5. Calati R, Giegling I, Rujescu D, Hartmann AM, Möller HJ, De Ronchi D, Serretti A. Temperament and character of suicide attempters. J Psychiatr Res., 2008; 42(11): 938-945.
6. Champagne FA, Curley JP. Epigenetic Influence of the Social Environment. In: Petronis A, Mill J, editors. Brain, Behavior and Epigenetics, Epigenetics and Human Health.

Berlin: Springer, 2011; 196-197.

7. Chapman AL, Dixon-Gordon KL. Emotional antecedents and consequences of deliberate self-harm and suicide attempts. Suicide Life Threat Behav, 2007; 37: 543-552.
8. Chen H, Wang N, Burmeister M, McInnis MG. MicroRNA expression changes in lymphoblastoid cell lines in response to lithium treatment. Int J Neuropsychopharmacol, 2009; 12: 975-981.
9. Courtet P, Gottesman II, Jollant F, Gould TD. The neuroscience of suicidal behaviors: what can we expect from endophenotype strategies? Transl Psychiatry [Internet]. May 2011. Available from www.nature.com/tp. [Last cited on July 01, 2014].
10. Dinan TG, Stanton C, Cryan JF. Psychobiotics: A Novel Class of Psychotropic. Biol Psychiatry, 2013; 74: 720-726.
11. Esquirol JE. Des Maladies Mentales. Paris: JB Bailliere, 1838.
12. Fawcett J. Diagnosis, Traits, States, and Comorbidity in Suicide. In: Dwivedi Y, editor. The Neurobiological Basis of Suicide. Boca Raton (FL): CRC Press, 2012: 1-8.
13. Feder A, Nestler AJ, Charney DS. Psychobiology and molecular genetics of resilience. Nat Rev Neurosci, 2009; 10(6): 446-457.
14. Fiori LM, Turecki G. Approaches and Findings from Gene Expression Profiling Studies of Suicide. In: Dwivedi Y, editor. The Neurobiological Basis of Suicide. Boca Raton (FL): CRC Press, 2012: 1-14.
15. Fiori LM, Zouk H, Himmelman C, Turecki G. X chromosome and suicide. Mol psychiatry, 2011; 16: 216-226.
16. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiat, 2003; 160(4): 636-45.
17. Gould E, Beylin A, Tanapat P, Reeves A, Shors, TJ. Learning enhances adult neurogenesis in the hippocampal formation. Nature Neuroscience, 1999; 2: 260-265.
18. Hawkins KA, Hames JL, Ribeiro JD, Silva C, Joiner TE, Cougle JR. An examination of the relationship between anger and suicide risk through the lens of the interpersonal theory of suicide. J Psychiatr Res., 2014; 50: 59-65.
19. Jokinen J, Nordström AL, Nordström P. CSF 5-HIAA and DST non-suppression orthogonal biologic risk factors for suicide in male mood disorder inpatients. Psychiatry Res., 2009; 165: 96-102.
20. Kirkcaldy BD, Siefen GR, Urkin J, Merrick J. Risk factors for suicidal behavior in adolescents. Minerva Pediatr, 2006; 58: 443-450.
21. Kong L, Chen K, Womer F, Jiang W, Luo X, Driesen N, Liu J, Blumberg H, Tang Y, Xu

K, Wang F. Sex differences of gray matter morphology in cortico-limbic-striatal neural system in major depressive disorder. J. Psychiatr. Res., 2013; 47: 733–739.

22. Kreitman N. The coal gas story. Unitted Kingdom suicide rates, 1960-71. British Journal of Preventing and Social Medicine, 1976; 30: 86-93.
23. Lanzenberger R, Baldinger P, Hahn A et al. Global decrease of serotonin-1A receptor binding after electroconvulsive therapy in major depression measured by PET. Mol Psychiatr, 2013; 18: 93-100.
24. Lee BH, Kim YK. Potential peripheral biological predictors of suicidal behavior in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry, 2011; 35: 842-847.
25. Mann JJ, Currier D. Medication in Suicide Prevention Insights from Neurobiology of Suicidal Behavior. In: Dwivedi Y, editor. The Neurobiological Basis of Suicide. Boca Raton (FL): CRC Press, 2012: 1-16.
26. McGirr A, Turecki G. What is specific to suicide in schizophrenia disorder? Demographic, clinical and behavioural dimensions. Schizophr Res., 2008; 98: 217–224.
27. Moller HJ, Rujescu D. Pharmacogenetics – genomics and personalized psychiatry. EUR J PSYCHIAT, 2010; 25: 291-293.
28. Olsson T, Mohammed AH, Donaldson LF, Henriksson BG, Seckl JR. Glucocorticoid receptor and NGFI-A gene expression are induced in the hippocampus after environmental enrichment in adult rats. Brain Res Mol Brain Res., 1994; 23: 349–353.
29. Ormel J, Oldehinkel AJ, Vollebergh W. Vulnerability before, during, and after a major depressive episode: A 3- wave population-based study. Arch Gen Psychiatry, 2004; 61: 990-996.
30. Painuly N, Sharan P, Mattoo SK. Antecedents, concomitants and consequences of anger attacks in depression. Psychiatry Res., 2007; 153: 39–45.
31. Pandey GN, Dwivedi Y. Neurobiology of Teenage Suicide. In: Dwivedi Y, editor. The Neurobiological Basis of Suicide. Boca Raton (FL): CRC Press, 2012; 1-13.
32. Perroud N, Neidhart E, Petit B, Vessaz M, Laforge T, Relecom C. et al. Simultaneous analysis of serotonin transporter, tryptophan hydroxylase 1 and 2 gene expression in the ventral prefrontal cortex of suicide victims. Am J Med Genet B Neuropsychiatr Genet, 2009; 153B(4): 909–918.
33. Pietersen CY, Lim MP, Woo TU. Obtaining high quality RNA from single cell populations in human postmortem brain tissue. J Vis Exp. 2009; 30: 1444.
34. Renthal W, Maze I, Krishnan V, Covington HE 3rd, Xiao G, Kumar A et al. Histone deacetylase 5 epigenetically controls behavioral adaptations to chronic emotional stimuli.

Neuron, 2007; 56: 517–529.

35. Roy A. Gene–Environment Interaction and Suicidal Behavior. In: Dwivedi Y, editor. The Neurobiological Basis of Suicide. Boca Raton (FL): CRC Press, 2012: 1-16.
36. Rujescu D, Giegling I. Intermediate Phenotypes in Suicidal Behavior Focus on Personality. In: Dwivedi Y, editor. The Neurobiological Basis of Suicide. Boca Raton (FL): CRC Press, 2012: 1-21.
37. Rutter M. Gene–environment interplay. Depress Anxiety, 2010; 27: 1–4.
38. Rutter M. Psychosocial Resiliences and Protective Mechanisms. Amer. J. Orthopsychiat, 1987; 57(3): 319-320.
39. Rutter M. Psychosocial Resiliences and Protective Mechanisms. Amer. J. Orthopsychiat, 1987; 57(3): 319-320.
40. Sarkar P, Sattar FA, Gode N, Basannar DR. Failed suicide and deliberate self-harm: A need for specific nomenclature. Indian J Psychiatry, 2006; 48: 78–83.
41. Silverman MM. Challenges to Classifying Suicidal Ideations, Communications, and Behaviours. In Editors: O'Connor RC, Platt S, Gordon J, editors. International Handbook of Suicide Prevention: Research, Policy and Practice, First Edition. John Wiley & Sons, Ltd. 2011; 14-16.
42. Treviño LJ, Fontecilla HB, Braquehais MD, Dominguez AH, Garcia EB. Endophenotypes and suicide behaviour. Actas Esp Psiquiatr, 2011; 39(1): 61-9.
43. Turecki G, Sequeira A, Gingras Y, Seguin M, Lesage A, Tousignant M. et al. Suicide and serotonin: Study of variation at seven serotonin receptor genes in suicide completers. Am J Med Genet B Neuropsychiatr Genet, 2003; 118B(1): 36–40.
44. Turecki G, Sequeira A, Gingras Y, Seguin M, Lesage A, Tousignant M. et al. Suicide and serotonin: Study of variation at seven serotonin receptor genes in suicide completers. Am J Med Genet B Neuropsychiatr Genet, 2003; 118B(1): 36–40.
45. Vinod YK. Role of the Endocannabinoid System in the Neurobiology of Suicide. In: Dwivedi Y, editor. The Neurobiological Basis of Suicide. Boca Raton (FL): CRC Press; 2012: 1-22.
46. Wilkinson MB, Xiao G, Kumar A, LaPlant Q, Renthal W, Sikder D et al. Imipramine treatment and resiliency exhibit similar chromatin regulation in the mouse nucleus accumbens in depression models. J Neurosci, 2009; 29: 7820–7832.
47. Wortzel HS, Beeta H, Matarazzo B, Brenner LA. Therapeutic Risk Management of the Suicidal Patient: Stratifying Risk in Terms of Severity and Temporality. J Psychiatr Pract, 2014; 20: 63-67.

48. Zalsman G. Genetics of Suicidal Behavior in Children and Adolescents. In: Dwivedi Y, editor. The Neurobiological Basis of Suicide. Boca Raton (FL): CRC Press, 2012; 1.