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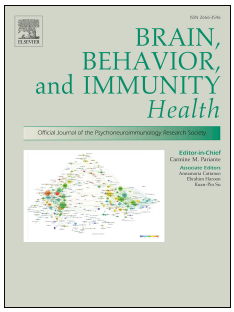

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Psychological and Neurobiological Aspects of Suicide in Adolescents: Current Outlooks

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Abstract:

Suicidality is one of the leading causes of death among young adults in the United States and represents a significant health problem worldwide. The suicide rate among adolescents in the United States has increased dramatically in the latest years and has been accompanied by considerable changes in youth suicide, especially among young girls. Henceforth, we need a good understanding of the risk factors contributing to suicidal behavior in youth. An explanatory model for suicidal behavior that links clinical and psychological risk factors to the underlying neurobiological, neuropsychological abnormalities related to suicidal behavior might predict to help identify treatment options and have empirical value. Our explanatory model proposes that developmental, biological factors (genetics, proteomics, epigenetics, immunological) and psychological or clinical (childhood adversities) may have causal relevance to the changes associated with suicidal behavior. In this way, our model integrates findings from several perspectives in suicidality and attempts to explain the relationship between various neurobiological, genetic, and clinical observations in suicide research, offering a comprehensive hypothesis to facilitate understanding of this complex outcome. Unraveling the knowledge of the complex interplay of psychological, biological, sociobiological, and clinical risk factors is highly essential, concerning the development of effective prevention strategy plans for suicidal ideation and suicide.

Keywords: suicide; psychology; neurobiology; immunology, clinical model; treatment

A. Introduction:

Suicide and Suicidal attempts in one of the major concerns in mental and public health issues worldwide(Curtin and Heron, 2019). Suicide is considered to be the second leading cause of death among youths in the United States and worldwide. According to the latest reports from the Center for Disease Control (CDC) and National Center for Health Statistics (NCHS) Data brief in 2019, suicide is the second leading cause of death for individuals aged 15–19 and 20–24 (Curtin and Heron, 2019). Based on the latest CDC reports a 30% increase in suicidal deaths were observed in the United States from 2000 to 2016, with increasing suicidal rates in all age groups (Miron et al., 2019). Conversely, adolescents are of major concern; the underlying causes or reasons could be increased usage of social media use, peer-pressures, depression, and anxiety. In 2017, 6241 suicidal deaths were reported in individuals aged 15 to 24 years, among those 5016 males and 1225 females (Curtin and Heron, 2019; Miron et al., 2019).

Based on the standpoint of public health and mental health issues, suicidality is one of the main issues to address through current preventive methods in adolescents (Miron et al., 2019). Suicide is a complex behavior with multiple factors associated with social isolation, mental illness, alcohol abuse, substance use disorder, family-related events (Esposito-Smythers et al., 2011; Ganz and Sher, 2009). Hence, it is highly important to gain insight into the plausible risk factors that contribute to suicidality in adolescents. In this review gives we tried to outline the most important risk factors-positive and negative as established by scientific research in this domain, biological, neurochemical, neurobiological, neuroimaging. Also, we tried to construct an explanatory integrative model for suicidality, clinical trials on suicidality, emphasizing the diagnosis, prevention, and treatment options available to combat suicide in youth and adults.

B. Scope of the problem: Adolescents at high risk

Early childhood adversity might be one of the potential risk factors that might impact the suicidal behavior (Mann, 2003). Adverse childhood events might include sexual abuse, physical abuse, child neglect, parental loss, and severe family discord, however, to date, physical and sexual abuse have been the focus of most studies (Mann, 2003). Childhood adversities are strongly linked to the emotional, psychological, suicidal ideation as early as during the gestational period (Monk et al., 2011).

i. Epidemiologic studies have, for many years, identified preterm birth as a significant risk factor for psychopathology in later childhood and adolescence. Perinatal factors have

long been implicated in the genesis of psychiatric disorders, but the role such factors play in the causal pathway is less well understood (Monk et al., 2011). Several reports from the literature have shown that newborns with low birth weight (<2500g) have significantly increased risk of major depression with suicidal ideation, anxiety disorders, phobias, and impaired functioning compared to those with normal birth weights (Nomura et al., 2007).

ii. Girls born late preterm and early term show an increased risk of emotional problems at 36 months of age. These finding suggests that gender should be taken into account when evaluating children who are born at these gestational ages (Stene-Larsen et al., 2016).

iii. Despite elevated rates of psychiatric disorders is associated with childhood among preterm children, it must be emphasized that most are found with other co-morbid conditions, and later environmental factors may also trigger the manifestations of these mental health disorders (Monk et al., 2011)..

iv. In the past few years, the number of suicidal adolescent deaths has increased dramatically in the United States. Adolescent males 15 to 19 years old were six times greater than the rate for females. The number of attempted suicides to completed suicides among adolescents is estimated to be higher among females than among males (Miron et al., 2019).

v. Alcohol use and alcoholism are also one of the potential risk factors for suicide in adolescents. Alcohol use has been strongly associated with 50% of suicides. Gay and bisexual adolescents are reported to display higher rates of suicidal ideation and suicidal behavior, also have major depression, suicidal attempts are 3 times higher than other adolescents.

C. Psychosocial Risk Factors of Suicidal Behavior in adolescents

1) Personality Risk Factors:

i) Hopelessness:

Hopelessness is considered as one of the risk factors for suicidality; however, it is also known to be associated with major depression; therefore hopelessness can be a contradictory factor when determining suicide risk by itself (Efstathiou et al., 2018; Wolfe et al., 2019; Young et al., 1996). Additionally, when looking at personality traits, this factor can itself be considered a risk for suicide. In other cases, it can be a co-risk paired with other influencing factors. Studies from the literature have shown that difficulties and during childhood will lead to hopelessness (Gaskin-Wasson et al., 2017).

ii) **Impulsivity**

Impulsivity is strongly associated with risky behavior management, psychopathology, and suicidality (Gvion, 2018). Several cross-sectional and longitudinal studies have been linked to suicide attempts with both self-reported and performance-based impulsivity in the adolescent population. Impulsivity has a positive correlation (Gvion, 2018). It is considered to be a promising risk factor for suicide (Coryell et al., 2018; Lewitzka et al., 2017; Singh and Rao, 2018; Wang et al., 2017).

iii) Aggression

Aggression, though a complex construct- is often associated with disruptive behaviors such as anger, victimization of peers, homicide isolation, and suicidal thoughts (Buchmann et al., 2014; Gvion, 2018). Aggression, commonly seen in adolescents (Buchmann et al., 2014) is one of the important risk factor for suicide, (Zhang et al., 2018) when it coexists with bullying (Shain and Committee On, 2016) (Klomek et al., 2009). Buchmann et al., (2014) have observed that impulsive aggression might be associated with suicidal behavior, as it relates to the stress-diathesis model of behavioral dysregulation during states of the strong negative effect that is common during the aggression (Buchmann et al., 2014).

iv) Perfectionism

High levels of perfectionism are positively associated with the increase risk of suicidal ideation and suicide attempts. Based on the literature, Smith et al., (2017) conducted a meta-analyses based on 45 different studies, that includes undergraduates, medical students, community adults, and psychiatric patients (n = 11,747) to understand the association between correlates of suicide and perfectionism(Smith et al., 2018). A total of 13 out of 15 perfectionism dimensions were positively associated with suicidal ideation (Beevers and Miller, 2004; Smith et al., 2018).

2) Cognitive factors

i) Cognitive rigidity: Cognitive rigidity is one of the positive characteristic risk factor for suicidal attempts and behavior (Neuringer, 1964; Perrah and Wichman, 1987). Cognitive rigidity leads to dichotomous thinking and categorizing all life experiences to either “good/bad”, “success/failure” According to Perrah and Wichman (1987) these two processes leads to nuances in acknowledging leads to problem-solving deficits and cognitive rigidity(Perrah and Wichman, 1987). Further,

neuropsychological studies have also shown that cognitive rigidity as a predictive cue for suicidal behavior (Neuringer, 1964; Perrah and Wichman, 1987).

ii) **Thought suppression:** Thought suppression is a potent mediator of emotional reactivity and self-injury(Pettit et al., 2009). Tucker et al. (Tucker RP, 2017) have shown that thought suppression unambiguously is strongly associated with suicidal behavior. Further studies from Najmi, Wegner, and Nock (2007) have shown suicide ideation, and at least one suicide attempt in adolescents reveal an increased propensity to suppress unwanted thoughts. Per the prior studies reported, Pettit et al. (2009) found a positive correlation between suicide ideation and thought suppression in subjects of undergraduate students and adolescent in-patients(Pettit et al., 2009).

iii) **Fearlessness and pain sensitivity:** In suicidal adolescents, self-injury is more common than in adults, and it can be due to an increase in pain tolerance (O'Connor et al., 2014). This increase has yet to be determined as either the source or the consequence of suicidal behavior (O'Connor and Nock, 2014; Orbach et al., 1997).

iv) **Agitation and Implicit associations:** Agitation and implicit cognitions are known to be projective behavior for suicide in people with suicidal ideations(Fawcett et al., 1997). Agitation is strongly linked to suicidal behavior in correlation to certain mental illnesses and medication as it can amplify negative symptoms and side effects. Close associations between the individual and death can be indicative of future suicide attempts in adolescents (Fawcett et al., 1997).

3) Social factors

Recent research examining trends of suicidal behaviors among adolescents of different racial and ethnic groups in the United States has shown an increase in suicide attempts among black youth with a significant increase in injury by attempts among black males (Lindsey et al., 2019, Pediatrics). The rise in the number of suicidal attempts is thought to be related to mental health and socio etiologic factors incommensurately experienced by black youth, including poverty and racial discrimination (Lindsey et al., 2019, Pediatrics). Stress-related to the aforesaid ethnicity groups including victimization is expected to account for their increased risk of suicidality (Thoma et al. 2019, Pediatrics).

i) **Social transmission:** Social or familial transmission occurs when a close family member attempted or committed suicide (Qin et al., 2002). Exposure to suicidal behavior can increase tendencies, especially if it comes from a maternal aspect.

Parental suicide has a more detrimental effect on children rather than in adolescents or adults (Qin et al., 2002) .

ii) **Social isolation:** Social isolation can be indicative of suicidal behavior because of the lack of support and the vulnerability of the individual to negative factors such as stress(Haw and Hawton, 2011). Besides, social media and networking have also shown a negative effect on adolescents and have led to self-harming and suicidal ideations. This factor is critical when analyzing suicidal behavior (Haw and Hawton, 2011; O'Connor et al., 2014). Social Isolation and social distancing during the COVID-19 pandemic have also shown increased risks for mental health issues such as fear, anxiety and increased suicidal risk (Ahorsu et al., 2020).

Positive Factors

i) **Optimism:** Hirsch and Conner et al., (2006) revealed that individuals with high confidence had a lower risk of developing suicidal behavior even when experiencing adverse life events. It is believed that optimism is a protective factor in lowering suicidal ideations (Hirsch and Conner, 2006).

ii) **Resilience:** Understanding and promoting the outcome of positive factors such as resilience might help to reduce the risk of suicidality. However, resilience solely cannot reduce the risk of suicidal behavior, Studies from Johnson et al., (2011) have shown that positive reinforcement might decrease the probability of developing suicidal behavior and have a positive impact on them (Johnson et al., 2011).

iii) **Problem solving and coping**: Problem solving appraisal factors such as confidence, approach-avoidance style, and personality control are the most strongly related to suicide ideation and hopelessness(Pollock and Williams, 2004). However, problem solving confidence might be associated with resilience which is important in coping with hopelessness and suicide (Guerreiro et al., 2013; Pollock and Williams, 2004). Problem-solving and coping have shown to have significant impact on suicidal behavior. While the direct relationship has yet to be described, changes in neurobiology are known to strongly influence this factor (Guerreiro et al., 2013; Pollock and Williams, 2004).

Negative life events

a. **Childhood adversities:** Early-life stress can lead to suicidal behavior. While the type of adversity affects the individual, the extent may vary according to the kind of stress

experienced. In other words, inevitable difficulties may be more detrimental than others, such as sexual and physical abuse. Suicidal behavior is significantly high in adolescents who experienced childhood adversities, and this behavior tends to decrease as age increases (Bruffaerts et al., 2010).

b. **Traumatic life events during adulthood:** While childhood adversities tend to increase suicidal behavior during adolescence, traumatic experiences can affect any individual at any age and could potentially lead to suicidal ideations (Stein et al., 2010).
c. **Physical illness:** Physical illness has been associated with suicidal behavior; however, the system of how it can influence the behavior has not been identified. It is hypothesized that physical illness can cause depression and therefore lead to suicide however, this has not been proven (Webb et al., 2012).

D. Neurochemical and neurobiological findings suicidal behavior:

Dopaminergic:

Dopamine (DA), a catecholamine synthesized in a two-step reaction process that involves the conversion of tyrosine into L-DOPA, a reaction catalyzed by the tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis (Nagatsu, 1991). In recent years, several reports describe a good correlation between dysfunction of dopaminergic functioning and suicide (Fitzgerald et al., 2017; Ho et al., 2018; Oquendo et al., 2014; Pizzagalli et al., 2019). The analysis of key dopaminergic markers such as the dopamine transporter (DAT) and dopamine receptors D1 and D2 revealed an imbalance in the D1 and D2 abundance in the dorsal striatum in suicide compared to controls, and a clear reduction in the amount of DAT and D1 appeared with age. Nonetheless, the mean receptor binding in the striatum was unchanged between suicide and controls (Fitzgerald et al., 2017). Interestingly, a reduction in dorsal striatal gray matter was observed in a group of adolescents with suicidal behavior, pointing to an important role of the dorsal dopaminergic system in vulnerability to suicide (Ho et al., 2018).

Serotonergic:

The serotonin or 5-hydroxytryptamine (5-HT) is a monoamine synthesized by the rate-limiting enzyme tryptophan hydroxylase (TPH1 and TPH2) from the amino acid tryptophan (Walther et al., 2003). It is implicated in a variety of functions in the nervous system such as mood and anxiety, sleep, aggressiveness, circadian rhythm, feeding, and social behavior, among many others. Not surprisingly, the serotonergic deficit is directly implicated in depression and compulsivity, leading to increased vulnerability to suicidal behavior in adolescents and

adults (Braquehais et al., 2012; Oquendo et al., 2014; Picouto et al., 2015). There is compelling clinical and genetic evidence that the serotonin transporter (SERT) plays a critical role in suicide. PET imaging in individuals with depression and who attempted suicide had a low abundance of SERT in the midbrain and higher serotonin$_{1A}$ receptor in the raphe nuclei (Miller et al., 2016; Oquendo et al., 2016). Likewise, postmortem brain tissue biochemical analysis has shown a reduction of SERT in the frontal cortex, hippocampus, and putamen; however, contradictory outcomes have been observed depending on the brain region analyzed (Purselle and Nemeroff, 2003; Steinberg et al., 2019). Besides, polymorphism at the transporter gene, particularly the polymorphism 5-HTTLPR predicts a three times higher-risk suicide compared to other alleles independent of age and sex (Daray et al., 2018; Nielsen et al., 2019; Sarmiento-Hernández et al., 2019).

Noradrenergic:

Noradrenaline also called norepinephrine (NE) is another catecholamine synthesized from tyrosine by TH and DDC enzymes and a final hydroxylation step of DA to produce noradrenaline by the enzyme dopamine β-hydroxylase (*DβH*) (Gonzalez-Lopez and Vrana, 2020). NE functions as a neurotransmitter in the central and peripheral nervous system, where it plays a role in regulating a variety of cognitive functions, motivation, and impulsivity, among others. Similar to serotonin, noradrenergic neurotransmission dysfunction is well established to contribute to depression and suicide, conforming the monoamine hypothesis (Benn and Robinson, 2017; Moret and Briley, 2011; Sasamori et al., 2019). Several polymorphisms have been identified at key components of the noradrenergic system such as *DβH,* norepinephrine transporter and NE receptors strongly associated to depression, addiction and suicide, either insertions, deletions or amino acid changes (Cao et al., 2018; Gonzalez-Lopez and Vrana, 2020; Hamner and Gold, 1998; Ueda et al., 2016; Zhou et al., 2015).

Hormonal changes:

Changes in the levels of the hormone are crucial for some individuals during suicidal behavior, especially in females. There is very interesting research regarding the menstrual cycle studying how feminine hormones fluctuate, thus affecting female behavior, which increases the risk for suicide (Owens and Eisenlohr-Moul, 2018). Association between premenstrual dysphoric disorder and suicide (Shams-Alizadeh et al., 2018) had been associated, and levels of some hormones in the reproductive cycle of females are risk factors for suicide. Other studies have shown that females with high levels of progesterone increase suicidal attempts (Mousavi et al., 2014). In adolescences, females that were under hormonal contraception had shown a positive

association between hormonal contraception and suicide. It concerns that conclusion from several studies indicated that adolescent females would have the highest risk of commit suicide under this hormonal contraception (Hughes and Majekodunmi, 2018; Owens and Eisenlohr-Moul, 2018; Skovlund et al., 2018).

E. Psychoneuroimmunological suicidal changes in adolescents

We reviewed research studies that concentrated on identifying certain proteins as biomarkers in adolescents that had committed suicide or with suicide ideations. One of the most accepted ideas is the dysregulation of the immune system, which was found in people with suicide attempts. Dysregulation of the immune system led to the hypothesis that cytokines are a risk markers for suicide in adolescence as early evidence suggested (Gabbay et al., 2009). Following this thought, data has shown that certain pro-inflammatory cytokines are risk markers for suicide (Pandey et al., 2012). A study conducted by Amitai (Amitai et al., 2019), measured cytokines in adolescent suicide victims and found elevated levels of cytokines in comparison to the control group (Amitai et al., 2019). The probable mechanism for an increase in the levels of inflammatory cytokine levels might be due to the activation of the Toll-like receptors (TLR) (Pandey et al., 2014). The toll receptors are known to play an essential role in regulating innate immune response and facilitating immune function in. So far, Pandey et al. (2014), have found that mRNA and protein levels of TLR3 and TLR4 were consistently dysregulated in suicidal subjects (Pandey et al., 2014). Based on the literature published so far, Inflammatory cytokines are interlinked with suicidal behavior by several mechanisms (Pandey et al., 2014). Inflammatory cytokines, like IFN-γ, IL-6, IL-1β, and TNF-α, are known to be affected by suicidal victims in adolescents. Apart from the cytokines involvement in contributing to the pathophysiology of suicidal behavior include activation of the kynurenine pathway, dysregulation of the HPA axis, and alterations in monoamine metabolism. QUIN, an N-methyl-D-aspartic acid receptor agonist and acts via activation of the NR1, NR2A, and NR2B NMDA receptors ((Jollant et al., 2020). Further, Tonelli et al. (2008) have reported that elevated mRNA transcripts of IL-4 and IL-13 in the orbitofrontal cortex of suicide victims (Tonelli et al., 2008). Besides, Steiner et al. (2008) demonstrated increased microgliosis is indicative of an enhanced inflammation in suicidality of the adolescent population (Steiner et al., 2008). Although there is limited data on postmortem data on teenage suicide victims also points to the association between inflammation and suicide. Pandey et al. (2010) reported that postmortem brain tissue from teenage suicide victims had increased mRNA and protein levels of IL-1β, IL-6, and TNF-α in cortical regions of Brodmann area 10 (Pandey and Dwivedi, 2010). Additional studies are

needed to support the relationship between inflammation and suicidality in youth either by meta-analyses. Together, these studies suggest that suicidality in adolescents might have an inflammatory signature irrespective of their primary diagnoses and other underlying conditions.

Steiner et al. (2006) first found the link between suicide and microglial activation, with HLA-DR as a microglial marker in suicidal victims (Steiner et al., 2006). No significant changes were observed in the cell-density of microglia; however, a substantial increase in the microglial density was found in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) of suicide victims (Steiner et al., 2008; Steiner et al., 2006). Schnieder et al. (2014) analyzed the microglial morphology with ionized calcium-binding adapter molecule 1 (Iba-1) and CD68 as microglial markers, interestingly, the density of Iba-1 activated microglia revealed significant effects in suicidal victims (Schnieder et al., 2014). Torres-Platas et al. (2014) conducted a case-control study using postmortem brains of suicide victims with major depression and control subjects (Torres-Platas et al., 2014). The ratio of primed over resting microglia was significantly increased in suicide victims with depression(Torres-Platas et al., 2014). Further, they found that the gene expression of Iba1 and MCP-1 was up-regulated considerably in suicide victims with depression. Brisch et al. (2017) revealed a significantly lower microglial reaction in depression who were not suicide victims; however, they found that increased microglial cell density was significant in the brains of suicide victims(Brisch et al., 2017).

Utilizing11C PET Imaging study, Holmes et al. (2018) conducted a case-control study to compare TSPO in ACC, PFC, and insula brain regions of MDD (n=14), controls (n=13) with moderate to severe depression severity (Holmes et al., 2018). They further conducted post hoc analysis to compare the TSPO availability between patients with and without suicidal thoughts(Holmes et al., 2018). Interestingly, TSPO was significantly increased in suicidal compared to non-suicidal subjects, most robustly in the ACC and insula(Holmes et al., 2018). Ernst et al. (2011) have shown a strong link between astrocytes and suicidality. Further, they have revealed that there is reduced expression of astrocyte connexins Cx30 and Cx43 in the DLPFC of suicide completers (Ernst et al., 2011). Nagy et al. (2018) showed decreased astrocytic conexin expression is associated with an altered chromatin state in the PFC region of suicidal victims (Nagy et al., 2018). Both CX30 and CX43 were down-regulated across several brain regions and that PFC tissue and repression of astrocytic connexins in cortical and subcortical brain regions and prefrontal enrichment were observed with H3K9Me3 in MDD and suicide (Nagy et al., 2018). These outcomes suggest a strong interlink between microglial and

astrocyte activation and suicide. However, furthermore extensive studies, including various, are needed to elucidate the relationship between microglia and astrocytes with suicide using novel methodologies and techniques, also beyond the psychiatric diagnostic boundaries.

F. Genetics and Epigenetics of Suicide in adolescents

Suicidal behavior in adolescences has not been thoroughly studied, and not many factors have been identified in this developing stage (Miron et al., 2019). Identifying markers can be useful in the prevention of suicide as they can serve as warning signs. Different factors can influence depression and suicidal behavior; the way the body responds to stress, genetics, epigenetics, and environmental factors are the most influential ones (Essex et al., 2013). Dysregulation of serotonin, HPA axis genes, and immune system in the human brain, especially in the frontal cortex, can affect human behaviors such as impulsivity, decision-making and mood and they have been strongly associated with the risk of suicidal behavior as they all play an important role in the body's response to stress (Roy et al., 2012). Also, childhood trauma can affect the normal function of some genes associated with the risk of committing suicide (Roy et al., 2012).

a. Genes involved in suicide in adolescents

Genetics plays an important role in everyday behavior, and there is no exception when it comes to suicidal behavior. All of the studies reviewed included childhood abuse and its correlation with altered genes. Dysregulation of the serotoninergic system, which combined with childhood abuse, can lead to suicidal behavior. In suicide victims, low levels of Brain-derived neurotrophic factor (BDNF) in the prefrontal cortex have been reported; impaired serotonin levels in this area can influence behaviors such as impulsivity, decision-making, and mood (Martinowich and Lu, 2008; Perroud et al., 2008). According to Roy (2012), the serotonin transporter 5-HTT is responsible for the absorption of serotonin back to the cell (Roy et al., 2012). In the serotonin transporter gene, the polymorphic area 5-HTTLPR can be influenced by environmental stressors and lead to suicidal behavior. This polymorphic region has two alleles that regulate gene transcription, s-allele, and l-allele. The s- allele decreases 5-HTT transcription efficacy as opposed to the l-allele. According to Lin and Tsai, 5-HTTLPR s-allele was more common in individuals that had attempted suicide. Decreased levels of BDNF, altered CRH and polymorphism in 5-HTTLPR influence decision making behavior in adulthood. These factors combined with childhood abuse can be directly linked to suicide in adolescents and they are summarized on *Table 1* (Guillaume et al., 2013; Martinowich and Lu, 2008; Perroud et al., 2008; Sarmiento-Hernández et al., 2019; Shinozaki et al., 2013).

b. Epigenetic markers for suicide in adolescents

The DNA and proteins in the chromatin can be modified to change the expression profile of genes in a very sophisticated process called epigenetics. One of the most studied and known modification is methylation and which is the addition of the methyl group(s) to either DNA or a protein in the chromatin, thus affecting gene expression (Greenberg and Bourc'his, 2019). Methylation in epigenetics has gotten significant attention because childhood stress/trauma exposure can result in changes in methylation of some genes involved in suicidal behavior in adolescences (Essex et al., 2013). Data has shown that corticotropin-releasing hormone (CRH) can have changes in methylation in adolescents with suicide attempts (Jokinen et al., 2018). Other non-adolescent research findings support this idea, as it states that there is an existing dysregulation on methylation in the prefrontal cortex in suicide human adult brains (Schneider et al., 2015). Changes of methylation of some genes could be used as a biomarker that can help determine which adolescences are at risk of committing suicide and therefore be able to prevent it. Regulation of gene expression at DNA levels due to chromatin remodeling and post transcriptional mechanisms are strongly linked to suicidality (Autry and Monteggia, 2009). Early life trauma has been associated with suicidal risk, and there is a strong association of epigenetics, which affects the functioning of several genes in the brain (Labonte et al., 2012). The vast amount of research in this area has been conducted in the adult brain, but in adolescences is rare. The hypothalamic-pituitary-adrenal (HPA) axis genes and proteins have being implicated to be dysregulated during childhood abuse/trauma, and genes for HPA-axis may be altered in suicidal idealization (Labonte et al., 2012). Several genes have been associated with risk for suicide in the HPA-axis, such as CRHBP and FKBP5 (Roy et al., 2012). Therefore, there has been an effort to understand the process involved in epigenetic on the HPA-axis genes. Indeed, Jokinen et al., (2018) they were able to identify a loci Cg19035496 at the promoted region of the CRH gene (Jokinen et al., 2018). Cg19035496 was hypermethylated in adolescents with a high psychiatric risk score, but in the same study with adults, they found that hypermethylation is associated with a high risk of suicide (Jokinen et al., 2018). Besides, Tanti et al., showed that history child abuse and trauma affected the DNA methylation of oligodendrocytes genes related to myelination such genes like LINGO3, POU3F1, and ITGB1 (Lutz et al., 2017). Labonte et al. (2012) observed changes in methylation levels in individuals with severe childhood abuse, especially hypermethylation of the promoter of the ALS2 gene, which decreases the transcription activity and expression of ALS2 gene isoform two at the hippocampus of victims of suicide (Labonte et al., 2012). Others examples are the kappa opioid receptor (Kappa) where the gene have lower methylation in victims of suicide with a history of

child abuse, neuron-specific glucocorticoid receptor (NR3C1) has increase methylation of NR3C1 promoter (Jokinen et al., 2018; Lutz et al., 2017).

G. Neuroimaging and Neurophysiology of suicidal behavior

Structural neuroimaging studies have shown that Prefrontal cortex (dorsal and ventral) changes are associated with suicidal thoughts and behavior; changes include reduced volumes and serotonergic dysfunction. Anterior cingulate cortex (dorsal and ventral) volumes are decreased in both adult and adolescents with a history of suicide attempts with major depressive disorder and bipolar disorder (Schmaal et al., 2020). Middle and superior temporal gyri volumes are lowered in high lethality suicidal attempters with high impulsive behavior across various mental disorders. Default network mode of the brain changes are associated with suicidal behavior in both adults and adolescents; changes are lower resting functional connectivity (Schmaal et al., 2020). Adolescents with suicidal attempts and bipolar disorder showed a decrease volume in the lateral orbitofrontal cortex, low 5-HT1a receptor binding and an increased lateral orbitofrontal cortex activation when regulating negative memories (Oquendo et al., 2016). Low volume of the dorsal and ventral anterior cingulate cortex in combination with mental disorders was associated with a higher attempt of suicide in adolescents (Wagner et al., 2011; Wagner et al., 2012). Suicidal ideations in adolescents showed an increase in activation in both the dorsal anterior cingulate cortex and dorsal lateral prefrontal cortex; this dysregulation can be due to the dorsal area of the brain being in charge of decision making and the control of emotions and behavior. Dolsen (2017) conducted a study in which it was hypothesized that hyperarousal during sleep correlated with suicidal ideations as well as a major depressive disorder(Dolsen et al., 2017). Neurophysiological hyperarousal occurs when the brain is at a constant state of high alert, which can lead to long-lasting stress. During sleep, hyper arousal can be reflected by an increased alpha and beta activity, as well as a slow frequency in delta activity (Dolsen et al., 2017). EEG studies on sleeping patterns have shown that neurophysiological hyper arousal during sleep may contribute to suicidal behavior when paired with major depressive disorder (Dolsen et al., 2017).

In *Figure-1,* we outline all the above sections into a integrative model to unravel the key target that needs to addressed in suicide research. An explanatory model that delineates neurodevelopmental, neurochemical, neuropsychological, clinical risk factors that are identified to be involved in suicidality. These biological (genetic, proteomics and epigenetics) and environmental factors might serve as endophenotypes and hold a strong interlink between them. Developing such putative models are highly important to understand the screening,

identifying targets that need further investigation to improve the process for prevention and treatment.

H. Clinical Trials on Suicidal Ideation and prevention in adolescents:

Based on the reports from clinical Trials.gov, we have tried to list the active clinical trials, the ones that are in progress, and completed. According to the clinicalTrials.gov database, there are 112 studies so far on suicidal ideation, attempts, and suicidality. Among those 42 studies are specific for suicidality in adolescents with youth (n=22 Trials); teens (n=8 Trials); adolescence (n=5 Trials); teenagers (n=2 Trials); which includes both currently existing ones and completed ones. Based on these, only 40 Clinical Trials on adolescents have been completed, and the results are available on the public domain. A list of these clinical Trials is listed here in the web link. https://clinicaltrials.gov/ct2/results?term=adolescents%2C+teenage&cond=Suicide&Search =Apply&recrs=e&age_v=&age=0&gndr=&type=&rslt=. The team led by Trivedi and colleagues conducted a clinical trial on Suicide Prevention and Resilience at Children's (SPARC). In essence, the purpose of this trial was to evaluate a set of interventions derived from a theory of suicide and compare their effects on outcomes (Jha et al., 2020). Also, it evaluates the effect of these interventions on reducing specific negative cognitions associated with depression and suicide ideation in an intensive outpatient program for suicidal youth.

I. Current and Future Strategies for Prevention, Intervention, and Treatment of Suicidality in Adolescents:

Effective mental health preventions, interventions may reduce the impact that mental health problems have on young people's well-being. Cultural considerations are warranted in the design of preventative interventions. Research has found substantial gender and racial/ethnic differences in suicide risk factors among youth underscoring the need for this (Lee and Wong, 2020). Recommendations for interventions tailored to the black community include efforts to increase access to mental health care by reducing stigma and increasing help-seeking behavior (Lindsey et al., 2019). Researchers examining risk and protective factors related to adolescent suicide attempts recommend psychotherapy aimed at treating persistent depression and increasing productive coping skills (Mirkovic et al., 2020).

Based on the meta-analyses from nine-different studies, Schimdt et al (2019) reported that all studies were based on school-based interventions, were carried out in the European Union. The interventions used were cognitive-behavioral therapy-based interventions aimed at the prevention of depression or anxiety, parenting program, a school-based social, emotional well-being program, and anti-bullying interventions sounds promising. Based on the literature- it

is also known that cognitive-behavioral sleep interventions might improve mental health in adolescents (particularly anxiety and depression) by improving sleep problems, since sleep is also a major risk factor for suicide.

Psychotherapy Interventions to prevent suicide in adolescents:

- *DBT for adolescents*

There have been multiple studies examining DBT adapted for adolescents (DBT-A) for the prevention of suicide and self-harm. A one-year randomized control study of DBT-A vs enhance treatment as usual noted a significant reduction in self-harm (which includes suicide attempts and nonsuicidal self-injury) during the study and at one year of follow-up. There was also a significant reduction in suicidal ideation in the intervention group, though this result did not carry through in the follow-up period (Mehlum et al., 2016).

- *Motivational interviewing-enhanced safety for adolescents*

Motivational interviewing has been postulated as a way to encourage behavioral change concomitantly with safety planning. A pilot study tested the feasibility of randomizing and using this technique (Czyz et al., 2019). Participants included adolescents between the ages of 13 and 17 who were hospitalized due to suicide risk. Motivational interviewing was used in addition to safety planning at discharge. Proximal outcomes in the MI group included greater likelihood in using coping and higher self-efficacy to refrain from suicide attempts. At 3 month follow-up however, it appears the intervention group had two more patients with suicide attempts compared to the control group. Four more patients in the intervention group were hospitalized compared to controls(Grupp-Phelan et al., 2019).

- Cognitive-Behavioral Therapies (CBT)

A 2017 randomized controlled trial involving adolescents aged 12-18 evaluated if a program called Safe Alternative for Teens and Youths (SAFETY) was effective in reducing suicide attempts in a participants that had attempted suicide or other means of self-harm 3 months prior (Asarnow et al., 2017). Patients received either the SAFETY protocol, which is a cognitive-behavioral dialectical behavior therapy-informed family treatment, or enhanced treatment as usual (E-TAU). This protocol involved utilizing two therapists (one for the participant and one for the parents) with an initial session at their home, creating a collaborative safety and treatment plan with all parties. Analyzing outcomes three months after the intervention, showed no suicide attempts in the SAFETY group and 4 in the E-TAU group. This

demonstrated an NNT of three, although there were no significant differences in non-suicidal self-injurious behaviors, and there were statistically significant higher ED visits in the SAFETY group.

Population and Universal Psychosocial interventions:

In 2019, Godoy Garraza, Kuiper, Goldston et al examined data from counties that received grants for suicide prevention in youths as part of the Garrett Lee Smith Youth Suicide Prevention Program (Godoy Garraza et al., 2019). Previous analyses had found this program, which involves training, outreach programs, and early intervention programs aimed at youths aged 10-24, was associated with a significant decrease one year after implementation of the program in counties compared to matched controls. However, this effect was not sustained 2 years or more after implementation (Godoy Garraza et al., 2015). This 2019 observational study further stratified counties into groups that used the programs for 1 years vs 2 years vs 3 years vs 4 years. They noted a greater association in the reduction of suicides in those counties that received GLS programs for a longer period. This association was statistically significant at the 1 and 2 year follow-up mark after programs had ended in those counties, with 0.893 fewer expected deaths by suicide per 100,000 and 1.095 fewer expected deaths by suicide per 100,000 respectively. This association was greatest in rural counties (where there were 2.4 fewer expected deaths). One limitation is that larger metropolitan counties in New England were excluded as adequate matched-controls were not available (Godoy Garraza et al., 2019). One large, multicenter, cluster-randomized controlled trial did find that a manualized, universal school-based intervention for pupils known as the Youth Aware of Mental Health Program (YAM) involving role-play with interactive workshops, booklets, and lectures about the risk of suicide and importance of mental health had a significant decrease in suicide and suicide ideation at 12-month follow-up with an odds ratio of 0.45 and 0.50 respectively (Wasserman et al., 2015).

Pharmacotherapy-based Interventions and Neuromodulation

- **Pharmacotherapy:**

  An open-label, single-arm study in adolescents aged 13-21 evaluated if N-Acetylcysteine (NAC) affected nonsuicidal self-injury (NSSI) (Cullen et al., 2018). Its exact mechanism is unknown; however, it has shown some utility in addiction and mood disorders. While NSSI is not the same as a suicide attempt, long term, there may be an association with suicide (Asarnow et al., 2011). Patients were titrated on NAC in two-week increments up to daily dosing regimen of 3600mg by weeks 5-8. At week 6 and week 8, there was a

statistically significant decrease in cutting episodes compared to baseline (Cullen et al., 2018). However, the secondary analysis showed that those who responded were those who had a higher baseline frequency of cutting episodes, and this effect was relatively small.

For Unipolar major depression or bipolar disorder, randomized trials have indicated that treatment with lithium can prevent suicidal behavior (Cipriani et al., 2013). A meta-analysis of four clinical trials (485 patients with either unipolar depressive disorders or bipolar disorder) compared lithium with placebo for continuation and maintenance treatment that ranged from 20 to 104 weeks (Cipriani et al., 2013; Cipriani et al., 2005); most patients had initially responded to acute treatment with open-label lithium (Cipriani et al., 2013; Cipriani et al., 2005). Though it is still unclear how lithium reduces the risk of suicide, lithium can prevent recurrence of mood episodes, and may also reduce aggression or impulsivity (Cipriani et al., 2013). Tricyclic antidepressants and monoamine oxidase inhibitors may be lethal if taken in high doses; they should be avoided if possible in the depressed patient who has expressed thoughts of suicide (Turecki et al., 2019; Yovell et al., 2016). By contrast, the SSRIs appear to be safer when taken in overdose and should be the drugs of choice in potentially suicidal depressed patients (Turecki et al., 2019; Yovell et al., 2016). Tricyclic and selective serotonin reuptake inhibiting (SSRI) antidepressants are known to lower the risk of suicide, one such SSRI like Vortioxetine, a new multimodal antidepressant, an antagonist to serotonin (5-HT) transporter, 5-HT3A, 5-HT7, and 5-HT1D receptor (Mazza et al., 2018). Mahabaleshwar et al., (2020) studies suicide-related events by post hoc analyses using 2 study pools (Mahableshwarkar et al., 2020): one short-term pool of 10 randomized, placebo-controlled studies (6–8 weeks) (N = 4990 patients) and another long-term pool (N = 1956 patients) that included three open-label extension studies (52 weeks) (Mahableshwarkar et al., 2020). Further, their detailed evaluations indicated that vortioxetine was not associated with an increased risk of suicidal ideation and behavior in adult patients with MDD (Mahableshwarkar et al., 2020).

Esketamine and Ketamine are utilized as possible treatments for acute suicidal ideation (Lengvenyte et al., 2019). Intranasal Esketamine is typically used for treatment-resistant depression, and intravenous Ketamine is a standard anesthetic drug (Lengvenyte et al., 2019). Ketamine, an N-methyl-d-aspartate glutamate antagonist agent, has recently hit the headlines because of its rapid antidepressant and concurrent anti-suicidal action (De Berardis et al., 2018; Lengvenyte et al., 2019). Clozapine, an

antipsychotic drug, is approved for the treatment of suicidal ideation in patients who have schizophrenia (Wilkowska et al., 2019). Although there is substantial evidence of these effects, to date, the mechanisms of anti-suicidal properties of clozapine are still elusive. Clozapine with its unique pharmacology, anti-aggressive and anti-impulsive properties reduces the suicidal ideation properties in bipolar patients (Wilkowska et al., 2019). Overall, Ketamine in the treatment of suicidal patients involves several pathways, most importantly, the glutamatergic system seems to play a pivotal role, and its dysregulation may be the basis of suicidal cognitive biases, explaining the benefits of ketamine treatment (De Berardis et al., 2018; Lengvenyte et al., 2019).

- **TMS:** ***rTMS for SI in adolescents open-label study***

  There was one exploratory study to see if there is an effect on Suicidal ideation (SI)in 19 patients aged 13-19 with a 30 treatment-course of acute repetitive Transcranial Magnetic Stimulation (Croarkin et al., 2018). Initially, there was a response for decreased SI, though further analysis adjusting for depressive symptoms severity found no statistically significant decrease in Columbia suicide severity scale Intensity of ideation score, nor in the "suicidality" item on the Children's Depression Rating Scale, Revised.

- **ECT:**

  One observational follow-up study examined the effects of ECT on adolescents at an academic medical center (Mitchell et al., 2018). Packets of questionnaires were sent to 117 patients who were less than 18 years of age at the time of receiving ECT, and of these, 25 returned the packets to the research team. Using the self-assessment suicide rating scale, 78.3% of participants indicated they had none or mild suicidality after treatment(Mitchell et al., 2018). While these findings are encouraging, there are no baseline measurements as to the patient's suicidality prior to starting treatment.

Emerging strategies and future options:

The Safety Planning Intervention is a structured intervention that utilizes a variety of techniques including prioritized coping strategies for individuals and social contacts, and when combined with structured follow-up, a randomized controlled trial found an association with a decrease in suicidal behaviors in an adult population in VA emergency departments (Stanley et al., 2018). Future studies could look at an adolescent population. Studies utilizing technology, such as smartphone application-based interventions, have shown promising, albeit limited

results. In 2018, the smartphone app BRITE was used in inpatient adolescents at discharge, however, while this RCT showed a trend towards a decrease in the occurrence of suicide attempts, these results were not significant, and there was no effect on suicidal ideation (Kennard et al., 2018). This does show promise for future studies aimed at using smartphone apps, particularly as according to the Pew Research Center, 95% of adolescents have access to a smartphone, and 45% surveyed noted they use them often (Monica Anderson, 2018). Some studies are currently underway looking at using apps in patients who may be a risk for suicide or self-harming behavior in participants receiving mental health treatment (Health, 2020). Other potential interventions include several different behavioral and psychological treatment modalities. Collaborative Assessment and Management of Suicidality (CAMS) has shown some limited evidence for adults (Hanratty et al., 2019), and there is currently a study looking at it as an intervention for children that are currently recruiting(Bridge, 2019). Other studies are looking at culturally informed CBT for specific patient demographics, including black and Latino youth (Hospital, 2020). Additional studies are looking at strategies that can be implemented at schools, in particular, to reduce suicide in those who identify as LGBTQ (Willging, 2019). There is currently a study examining the effects of single-dose ketamine in adolescents with depression and anxiety (Bloch, 2019). As there is some evidence that it can decrease suicidality in adults, if proven safe and effective for adolescents, this opens another treatment modality to prevent suicide ideation and attempts in children.

Conclusions: Major depression in youth is one of the significant risk factors for suicidal behavior. Henceforth, we need a good understanding of the risk factors contributing to suicidal behavior in youth. In the present review, we have summarized and critically discussed studies related to clinical and neurobiological factors related to suicide in adolescents. Our review focusses explicitly on the explanatory model for suicidal behavior that links clinical and psychological risk factors to the underlying neurobiological, neuropsychological abnormalities related to suicidal behavior might predict to help identify treatment options and have empirical value. Our explanatory model proposes that developmental, biological factors (genetics, proteomics, epigenetics, immunological) and psychological or clinical (childhood adversities) may have causal relevance to the changes associated with suicidal behavior. In this way, our model integrates findings from several perspectives in suicidality and attempts to explain the relationship between various neurobiological, genetic, and clinical observations in suicide research, offering a comprehensive hypothesis to facilitate understanding of this complex outcome. Unraveling the knowledge of the complex interplay of psychological, biological,

sociobiological, and clinical risk factors is highly essential, concerning the development of effective prevention strategy plans for suicidal ideation and suicide. Another focus of our review is the discussion of possible similarities and differences in the neurobiological abnormalities between adults and suicidality in adolescents. Studies of the brain or postmortem brain are more appropriate for studies of suicide neurobiology, even though they may have many limitations. Future research should emphasize on identifying the underlying mechanisms of suicidal thoughts and behaviors that are specific to adolescent populations. This knowledge would greatly help us in understanding the progression of the disease, early diagnoses, interventions that specifically address issues like impulsivity, aggression, reduced positive affect, lack of social interaction, increased negative thoughts, poor distress tolerance, and family interactions in suicidal adolescents. This information will facilitate generating treatment strategies that are more effective in reducing suicidal thoughts and behaviors in adolescents.

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Figure Legends:

Figure 1: An integrative explanatory model of suicidality in adolescents.

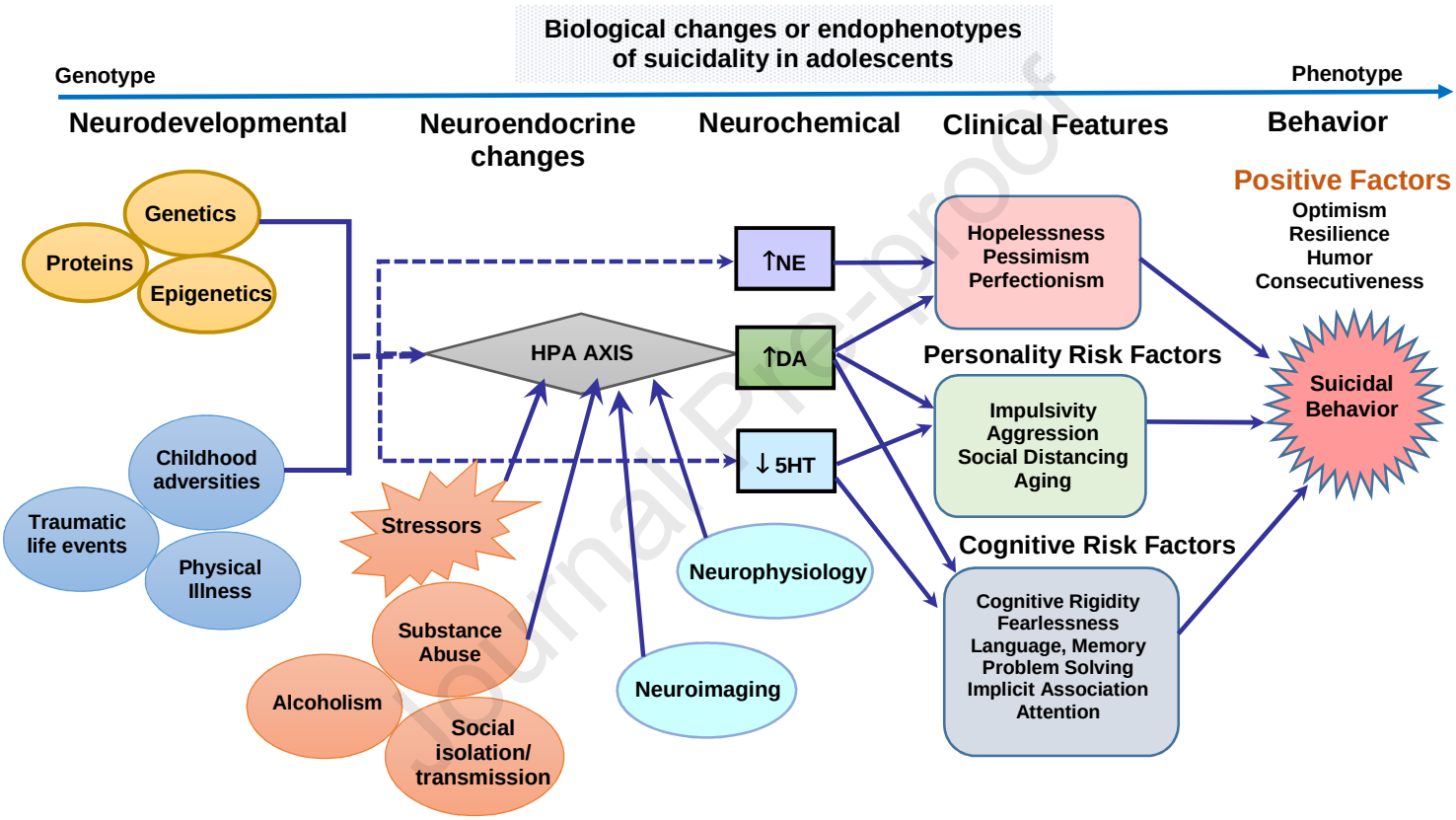

Table 1: List of major protein, epigenetic and genetic markers that are associated with suicidality in adolescents.

Type	Study	Marker	Method	Study findings	Sample source
Protein	(Amitai et al., 2019)	IL-6	ELISA	High levels of IL-6 were found to be a risk factor for fluoxetine-associated suicidality. Subjects in this study were with an average age of 13.9 years.	Plasma
Protein	(Pandey et al., 2013)	GR-α	Western blot	GR-α, protein, and mRNA were low in the prefrontal cortex and amygdala of adolescent suicide victims.	Postmortem brain
Protein	(Pandey et al., 2012)	IL1-β, IL-6, and TNF-α	Real-time PCR and ELISA	Levels of mRNA and Protein for IL1-β, IL-6, and TNF-α were high in postmortem brains from suicide subjects. Subjects in this study were aged from 13-20 years.	The prefrontal cortex (human brain)
Protein	(Gabbay et al., 2009)	TNF-α and IFN-γ	ELISA	Subjects with suicide-MDD had lower TNF-α levels compared to MDD. IFN-γ was higher in suicide compared to no suicide group. Subjects in this study were 14-19 years.	Plasma
Lipid	(O'Connor et al., 2018)	Cortisol	Elisa	The study was conducted with adolescents and adults (18-62 years). Individuals with childhood trauma and with any history of suicide had low levels of cortisol.	Saliva
Epigenetics	(Jokinen et al., 2018)	DNA Methylation	Methylation profiling	Data show hypermethylation of corticotropin-releasing hormone (CRH) in adolescents with high general psychiatric risk.	Blood
Epigenetics	(Essex et al., 2013)	DNA Methylation	Microarray	The author proposed, based on their data, an association between adversities in early childhood and DNA methylation.	Buccal epithelial cells
Genetics	(Sarmiento-Hernández et al., 2019)	Polymorphism 5-HTTLPR	PCR	This study was conducted in a Mexican population of adolescents who found a high prevalence of “SS” and “S” genotype for 5-HTTLPR in a population with history of depression and suicide.	Blood
Genetics	(Guillaume et al., 2013)	Polymorphism of the genes CRHR1 and CRHR2	Genotyping by PCR	Polymorphism in genes CRHR1 and CRHR2 may be implicated in suicide.	Blood
Genetics	(Roy et al., 2012)	Polymorphism of CRHBP	Genotyping using Illumina	Childhood trauma increases the risk of suicide as well as variation in the CRHBP gene	Blood
Genetics	(Perroud et al., 2008)	Polymorphism of BDNF: Val66Met	Genotyping by PCR	Based on their data, they concluded that childhood abuse, besides with BDNF Val/Val genotype, is a high risk for a person to commit violent suicide.	Peripheral lymphocytes
Genetics	(Roy et al., 2007)	Polymorphism 5-HTTLPR	Genotyping	5-HTTLPR genotype (low expressing) is a risk marker for suicide.	Blood

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Highlights:

- Suicidality, suicidal attempts in adolescents is currently one of the major concern in public and mental health issues worldwide.
- Positive and Negative symptoms of suicide in adolescents.
- Neuropsychology, neurobiology- neurochemical, neuroimmunological and sociobiological risk factors of suicidality in adolescents.
- Early risk assessments and its impact on treatment strategies for suicide.

Conflict of Interest:

No conflict of interest related to this manuscript.

Credit Author Statement

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