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Biological Prediction of Suicidal Behavior in Patients with Major Depressive Disorder

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1. Introduction

Suicide is a major public health issue and a significant cause of death worldwide. Most suicides (about 90%) occur in the context of psychiatric disorders, most commonly major depressive disorder, which is associated with approximately 60% of all suicides (Carlson et al. 1991). Prediction of suicidal risk in major depressive disorder is very important for preventing suicide, but current approaches to predicting suicidal behavior are based on clinical history and have low specificity. Accordingly, biological markers may provide a more specific means of identifying individuals at high risk of suicide with major depressive disorder (Lee and Kim 2011). Despite the high lifetime rate of suicide in patients with major depressive disorder (estimated to be 10-15%; Wulsin et al. 1999), most never attempt suicide. This raises the question of why some people with major depression are at risk of suicide and others are not, and suggests that the predisposition toward suicidal behavior is independent of psychiatric disorders. Other factors that increase the risk of suicidal behavior include psychosocial stressors, aggressive and impulsive traits, hopelessness, pessimism, substance abuse and dependence, physical or sexual abuse during childhood, and a history of head injury or neurological disorders. In considerations of these risk factors, suicidal behavior has been conceptualized into stress-diathesis and state-trait interaction models (Mann et al. 1999; Van Heeringen and Marusic 2003). Figure 1 illustrates the stress-diathesis model of suicidal behavior.

These models suggest that acute psychological stressors act on the diathesis, or traits of suicidal behavior, and that the complicated interactions between stress and diathesis gradually evolve into suicidal behavior over time. Previous research has explored potential biological markers and predictors of suicide and suicidal behavior, especially in the context of major depression. Although work in this area has been inconclusive, many animal, post-mortem, clinical, and genetic studies have produced results implicating at least 3 neurobiological systems in the pathogenesis of suicidal behavior in major depression: deficiency in the serotonergic system, hyperactivity of the hypothalamic-pituitary-adrenal axis, and decreased brain derived neurotrophic factor (BDNF) metabolism. Additionally, other neurotransmitters, cholesterol, nitric oxide (NO) and cytokines may be associated with suicide and suicidal behavior in major depression. Specifically, diathesis or trait-dependent risk factors are associated with dysfunctions in the serotonin system; however, the stress response (i.e., state-dependent factors) is related to hypothalamic-pituitary adrenal(HPA)

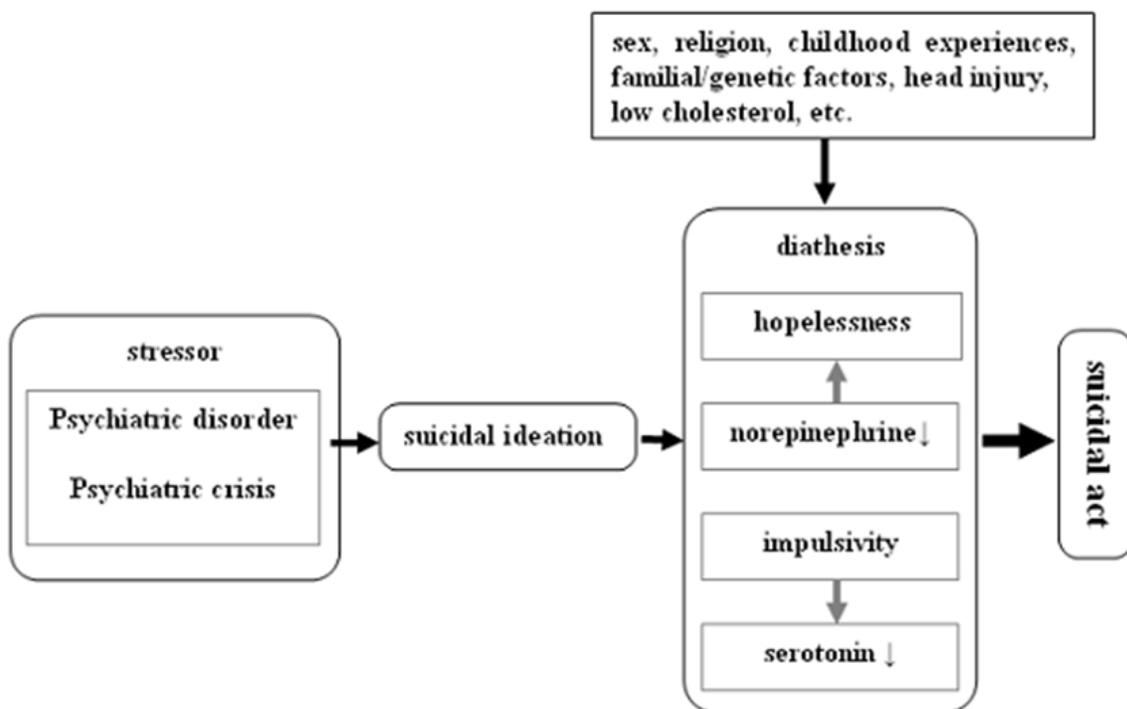


Fig. 1. Stress-diathesis model of suicidal behavior

axis hyperactivity. Decreases in cholesterol and BDNF levels are associated with impaired brain plasticity among individuals with suicidal behavior in major depressive disorder. In this chapter, I discuss peripheral biological markers involved in the pathogenesis of suicidal behavior in major depressive disorder and propose a model to predict the risk of suicidal behavior in these patients.

2. The neurotransmitter system

2.1 Serotonin

The serotonin system has been widely investigated in studies of major depression and suicide. The innervations of the serotonin system project from the dorsal raphe nucleus to all of the regions of the brain, including the cerebral cortex and hippocampus. Decreased function and activity of the serotonergic system in suicide victims and patients with major depression who attempt suicide have been confirmed in postmortem, serotonin transporter, serotonin receptor and cerebrospinal fluid (CSF) studies and neuroendocrine challenge tests. Post-mortem studies of the brains of suicide victims provide evidence of reduced serotonin transporter sites in the prefrontal cortex, hypothalamus, occipital cortex and brainstem (Purselle and Nemeroff 2003). In an autoradiographic study, this abnormality was found to be localized to the ventromedial prefrontal cortex (Arango et al. 1995). Abnormalities were also observed at the receptor level, as postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors were found to be upregulated in the prefrontal cortex. It has been hypothesized that this increase may be a compensatory mechanism to counter the low activity of serotonergic neurons (Mann 2003). It is interesting to note that this serotonin dysfunction appears to be localized to the ventral prefrontal cortex, a region that is involved in behavioral and cognitive inhibition. Thus, low serotonergic input may contribute to impaired inhibition, creating a greater propensity to act on suicidal or aggressive feelings (Mann 2003).

Tryptophan hydroxylase (TPH), which has two isoforms (TPH1 and TPH2), is one of the rate limiting factors in serotonin synthesis. Postmortem studies have reported significantly higher numbers and higher densities of TPH immunoreactive neurons in the dorsal raphe nuclei of depressed suicide victims (Underwood et al. 1999) and in the same regions of alcohol dependent, depressed suicide victims (Bonkale et al. 2006) when compared to controls. We have found that the TPH2 -703G/T SNP may have an important effect on susceptibility to suicidal behavior in those with major depressive disorder. Additionally, an increased frequency of the G allele of the TPH2 SNP is associated with elevated risk of suicidal behavior itself rather than with the diagnosis of major depression, and may increase the risk of suicidality, independent of diagnosis (Yoon and Kim 2009). Collectively, TPH, serotonin transporter, and serotonin receptor studies suggest that deficient or impaired serotonin activity is involved in suicidal behavior. Increased activity in TPH and postsynaptic 5-HT_{2A} receptors may be compensatory results of decreased central levels of serotonin. Notably, serotonin dysfunction appears to be localized in the ventral prefrontal cortex among suicide victims (Mann et al. 2000), as well as in individuals who make suicide attempts (Leyton et al. 2006).

The prefrontal cortex has been implicated in both behavioral and cognitive inhibition, as well as in willed action and decision-making. A meta-analysis examining 27 prospective and retrospective reports found that individuals who attempt suicide, and particularly those who use violent methods, had lower cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) levels when compared to psychiatric controls (Lester 1995). Additionally, a meta-analysis of prospective biological studies estimated the odds ratio for the prediction of suicide completion to be 4.5-fold greater for individuals with low levels of CSF 5-HIAA than individuals with high levels of CSF 5-HIAA among patients with mood disorders (Mann et al. 2006). CSF 5-HIAA may serve as a predictor of future suicide attempts and completions, as findings associating CSF 5-HIAA levels with suicidal behavior have been relatively consistent. Additionally, levels of CSF 5-HIAA are relatively stable and therefore believed to be under substantial genetic control (Rogers et al. 2004). Blunted prolactin response to the fenfluramine challenge test has been observed among young (<30 years) inpatients with major depression and histories of suicide attempts (Mann et al. 1995). Other work has shown significantly lower prolactin responses to fenfluramine challenge tests among depressed patients with histories of suicide attempts than among patients without such histories or healthy controls (Correa et al. 2000; Mann et al. 1995). Further, decreased prolactin response has been reported among patients with histories of high-lethality suicide attempts (Malone et al. 1996). These results suggest that blunted prolactin response to fenfluramine, which indicates reduced serotonin function, may serve as a marker for suicidality among individuals with major depressive disorder.

2.2 The noradrenergic and dopaminergic systems

Few post-mortem studies have examined alterations in the noradrenergic or dopaminergic systems in suicide victims. Studies have found decreased noradrenalin (NA) levels in the brainstem and increased α ₂-adrenergic receptor densities in suicide victims (Ordway et al. 1994a). One study found that tyrosine hydroxylase (TH), the rate-limiting enzyme for NA and dopamine (DA) synthesis, is higher in suicide victims (Ordway et al. 1994b), however another study found the opposite (Biegon and Fieldust 1992). Increased TH and α ₂-

adrenergic receptor densities could be indicative of noradrenergic depletion compensatory to increased NA release. Increased NA release may be explained by the relationship between the noradrenergic system and stress response, as severe anxiety and agitation are associated with noradrenergic overactivity, higher suicide risk, and overactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Mann 2003).

Few studies have examined the dopaminergic system. Overall, no alterations were found in mRNA levels of the D1, D2 and D4 receptors that bind in the caudate nuclei of suicide victims (Hurd et al. 1997; Sumiyoshi et al. 1995). A recent investigation exploring homovanillic acid (HVA) in the CSF of depressed suicide attempters found reduced HVA levels in attempters, but not in depressed non-attempters (Sher et al. 2006). Thus, the dopamine system seems to be hypofunctional in major depression (Kapur and Mann 1992).

3. Neurotrophic factors

3.1 Brain derived neurotrophic factor (BDNF)

Neurotrophic factors including BDNF, nerve growth factor (NGF) and neurotrophin (NT)- 3, 4/5, play an important physiological role in the maintenance and growth of neurons and synaptic plasticity in the adult brain (Lewin and Barde 1996) and are known to be involved in the pathogenesis of depression and suicide (Duman et al. 1997; Nestler et al. 2002). In particular, BDNF mRNA expression levels are significantly decreased in animals subjected to forced swimming and chronic immobilization stress (Russo-Neustadt et al. 2001; Xu et al. 2002). Moreover, chronic antidepressant treatment increases the expression of BDNF and neurogenesis in adult rat hippocampi (Duman et al. 1997; Malberg et al. 2000). Several clinical studies have found differing BDNF levels in the blood sera or plasma of patients with major depression and patients who have attempted suicide. Deveci and colleagues (2007) investigated serum BDNF levels among suicide attempters without major psychiatric disorders, patients with major depression, and healthy subjects. They found that serum BDNF levels were lower among both suicide attempters and depressed patients than among healthy controls. Our research group has also examined plasma BDNF levels among patients with major depression who both have and have not attempted suicide. One study found that plasma BDNF levels were significantly lower among depressed patients than among normal controls (Lee et al. 2007). Plasma BDNF levels were also significantly lower among suicidal patients than non-suicidal patients with major depression, and that suicidal patients had the lowest levels of BDNF among all of the groups assessed (Lee et al. 2007). Further, Kim and colleagues (2007b) measured plasma BDNF levels in patients with depression who had recently attempted suicide, non-suicidal patients with depression, and healthy controls. BDNF levels were significantly lower among suicidal patients with depression than non-suicidal patients with depression and healthy controls. However, BDNF levels did not differ between individuals who made fatal and nonfatal suicide attempts (Kim et al. 2007b). One study examining BDNF mRNA expression in peripheral blood mononuclear cells revealed that patients with major depression and recent suicide attempts had decreased BDNF mRNA expression, compared to patients who had not attempted suicide (Lee and Kim 2010). Measurements of BDNF levels in sera or plasma in previous studies have been challenged, as it is questionable whether BDNF in the blood is released from the brain or from other sources. To address this issue, Dawood and colleagues (2007) used direct blood sampling from the internal jugular vein and the brachial artery and

found that veno-arterial BDNF plasma concentration gradient acts as an index of brain BDNF production. Based on this determination, the veno-arterial BDNF concentration gradient was shown to be significantly reduced among patients at medium to high suicide risk compared to those at low risk. Additionally, this gradient was negatively correlated with suicide risk among untreated patients with depression. As such, BDNF level in sera or plasma appears to be decreased among suicidal individuals soon after attempted suicide, which is consistent with the changes observed in brain BDNF levels that have been reported in postmortem studies. These results suggest that BDNF may play an important role in the neurobiology of suicide and suicidal behavior in major depression.

3.2 Other neurotrophic factors

One study has found that BDNF and neurotrophin-3 (NT-3) levels are decreased in postmortem brains of suicide victims (Karege et al. 2005). Additionally, mRNA levels of nerve growth factor (NGF), NT-3, NT-4/5, cyclophilin, and neuron-specific enolase are decreased in the hippocampi of suicide victims (Dwivedi et al. 2005). Few studies have investigated other neurotrophic factors, and further studies in suicidal depression are necessary.

4. The hypothalamic–pituitary–adrenal (HPA) axis and cortisol

The HPA axis is the major biological system involved in the acute stress response. The stress-related theory of depression states that chronic stress may lead to long-term activation of the HPA axis, which may then result in reductions in the volume or impairments to the function of the hippocampus (Holsboer 1988). Corticotropin-releasing hormone (CRH) levels in the CSF tend to be increased among suicide victims, suggesting an increase in HPA axis activity among individuals with suicidal behaviors (Arato et al. 1989). However, this association remains controversial and other research has shown that patients who make repeated suicide attempts may have even lower CSF CRH levels than patients who do not (Traskman-Bendz et al. 1992).

The dexamethasone suppression test (DST) is one of the most useful assessments of HPA axis activity. During normal HPA axis activity, administration of dexamethasone, an exogenous synthetic glucocorticoid hormone, leads to negative feedback to the HPA axis. This negative feedback results in suppression of the release of adrenocorticotrophic hormone (ACTH) from the hypothalamus, which results in suppression of the release of cortisol from the adrenal gland. The reduction in cortisol levels as measured in plasma results in a positive result on the DST test. Many studies have shown that cortisol non-suppression in response to the DST is a strong predictor of suicidal behavior (Coryell and Schlessler 2001; Kunugi et al. 2004; Yerevanian et al. 2004). Specifically, some reports have demonstrated that patients with non-suppression engage in more serious suicide attempts (Coryell 1990; Norman et al. 1990) or use more violent methods (Roy 1992) than those who do not exhibit non-suppression. Jokinen and Nordström (2008) found that DST non-suppression is associated with suicide attempts among young adult and elderly inpatients with mood disorders. However, Black and colleagues (2002) found no significant differences in the frequency of suicidal ideation or completed suicides between patients demonstrating DST suppression and those demonstrating non-suppression (Black et al. 2002). A long-term follow-up study spanning 15 years has shown that patients with depression and DST non-

suppression have a roughly 14-fold higher risk of suicide than do patients with DST suppression (Coryell and Schlessler 2001). A meta-analysis estimated the odds ratio of suicide completion to be 4.5-fold greater among non-suppressors than suppressors in patients with mood disorders (Mann et al. 2006). Moreover, other long-term follow-up studies have suggested that the DST is a useful predictor of suicidal behaviors and attempts among individuals with mood disorders, depressed inpatients, and patients with manifest suicidality, but not among the general population (Jokinen et al. 2007) or in patients displaying DST suppression (Coryell et al. 2006). Further, Jokinen and colleagues (2008b) suggested that a different threshold for cortisol levels following dexamethasone may require defining DST non-suppression for the prediction of suicide among individuals experiencing melancholic depression. Yerevanian and colleagues (2004) also reported that DST non-suppression identifies unipolar depressed patients at higher risk of future suicide completion or hospitalization for suicidality. Overall, evidence suggests that HPA axis hyperactivity may influence the overactivity of the adrenergic system and alternations of the serotonergic system (Mann 2003; Meijer and de Kloet 1998).

5. Cholesterol

Trials of cholesterol-lowering drugs revealed increased mortality due to accidents, violence, and suicide among subjects who received the drugs (Kaplan et al. 1997; Muldoon et al. 1990). Kaplan and colleagues (1997) suggest that serum cholesterol reduction achieved by changing the serum composition or concentration of lipoproteins, could affect brain levels of fat-soluble micronutrient supply, structural lipids, cellular communication, or neurotransmitters, including serotonin. However, a second meta-analysis revealed only a modest, non-significant increase in deaths due to suicide and violence among patients receiving trials of dietary interventions and non-statin drugs (Muldoon et al. 2001).

Clinical studies of psychiatric subjects indicate a relationship between lower total cholesterol levels and suicidal behavior. Specifically, it has been reported that suicide attempters tend to have significantly lower cholesterol levels than non-suicidal psychiatric inpatients and individuals experiencing accidental injuries (Kunugi et al. 1997). Plasma cholesterol levels among acutely suicidal patients with mood disorders were found to be lower than among non-suicidal inpatients with mood disorders and healthy subjects (Papassotiropoulos et al. 1999). Additionally, a study of serum cholesterol levels showed that serum cholesterol is 30% lower among violent suicide attempters, in comparison to non-violent suicide attempters and healthy subjects (Alvarez et al. 2000). Of note, studies of Korean subjects found that serum total cholesterol levels and densities of lipoproteins tend to be lower among parasuicidal individuals, and that serum triglyceride levels tend to be lower among suicide attempters than non-suicidal patients with major depressive disorder (Kim et al. 2002a; Lee and Kim 2003). Moreover, our data suggest two cut-off points for serum cholesterol levels in patients with depression: 180 mg/dl, which may serve as a point for high sensitivity of possible risk of suicide, and 150 mg/dl, a point with a high specificity of probable risk of suicide (Kim and Myint 2004). However, studies in the general Korean population have failed to report consistent findings linking low cholesterol levels and suicidal behavior (Ellison and Morrison 2001; Iribarren et al. 1995). If suicidal behavior is associated with reductions in serum or plasma cholesterol levels, this may be explained because low cholesterol levels are related to decreased serotonin activity, which may increase tendencies toward impulsive, aggressive, and suicidal behavior (Heron et al. 1980;

Kaplan et al. 1997; Ringo et al. 1994). Another possible explanation is that decreased cholesterol in peripheral blood may reduce cholesterol levels in the brain, which may lead to reduced synaptic plasticity and brain dysfunction associated with impaired neurobehavioral consequences (Mauch et al. 2001; Pfrieger 2003).

6. Nitric oxide and cytokines

Nitric oxide (NO) is an endogenous gas that is known to influence cerebral monoaminergic activity, including serotonin activity (Montague et al. 1994; Yamada et al. 1995). In patients with major depression, the total amount and density of neurons with immunoreactivity to nitric acid synthase (NOS) were reduced in paraventricular neurons (Bernstein et al. 1998), and NOS activity was decreased in the prefrontal cortex (Xing et al. 2002). A previous study revealed that plasma NO levels were dramatically lower in patients with major depressive disorder compared to healthy controls (Chrapko et al. 2004). However, another study detected elevated NO levels in patients with major depression compared to patients with anxiety disorder and normal control subjects (Jozuka et al. 2003). We found that increased NO production in plasma is associated with suicide attempts in depressed patients (Kim et al. 2006).

It has been postulated that major depression is accompanied by significant changes in cell-mediated and humoral immunity and that these changes are related to the pathophysiology or pathogenesis of the illness (Miller and O'Callaghan 2005; Myint and Kim 2003; Schiepers et al. 2005). Pro-inflammatory cytokines including IL-1 β , IL-6, IL-12, and TNF- α are increased in the blood in major depression (Kim et al. 2002b; Thomas et al. 2005; Tuglu et al. 2003; Viljoen and Panzer 2005). These findings suggest that innate immunity is activated by secretion from monocytes and macrophages during major depression. A previous study measured cytokine secretion of T-cells of suicidal and non-suicidal depressed patients and healthy controls and found that the T-cells of suicidal depressed patients have Th1 characteristics, while the T-cells of non-suicidal depressed patients have Th2 characteristics (Mendlovic et al. 1999). A new hypothesis concerning the relationships between serum lipids, depression, suicide and atherosclerosis suggests that IL-2 plays important roles in lipid metabolism, depression, suicide and atherosclerosis (Colin et al. 2003; Penttinen 1995). Our group found that Th1 and Th2 cytokine imbalances are observed in a subpopulation of depressed patients (Myint et al. 2005). We also found that Th1 cytokine (IL-2 and IL-6) levels were significantly lower in suicidal depressed patients than in non-suicidal depressive patients and normal controls (Kim et al. 2007a). Collectively, NO and cytokines may be candidates for biological markers of suicidal behavior in major depression, but they have not yet been investigated extensively.

7. Can we predict suicidal behavior in major depression?

Many studies have tried to identify biological etiologies and predictors of suicidal behavior in major depression, but this task has been difficult because most suicide risk factors have low specificity and the rate of suicide completion is relatively low in the general population (Cohen 1986). These difficulties can be addressed when combinations of risk factors for suicide are used to estimate the suicide risk of individuals. For instance, several researchers have examined combinations of two biological risk factors for suicide simultaneously. Specifically, researchers have studied the coupling of CSF 5-HIAA and DST

non-suppression (Jokinen et al. 2008a; Jokinen et al. 2009; Mann et al. 2006) and the coupling of serum cholesterol and DST non-suppression (Coryell and Schlessner 2007). These combined factors may be useful because they reflect diverse aspects of suicidal phenomena. Specifically, Jokinen and colleagues (2008a) suggest that CSF 5-HIAA and DST non-suppression are independent biomarkers and that CSF 5-HIAA may reflect short-term suicide risk, while dysregulation of the HPA axis may be a more long-term predictor of suicidal behavior. These findings appear to be even better predictors among individuals with major depression or with previous histories of attempted suicide. Mann and colleagues (2006) also suggested that low CSF 5-HIAA and serotonin dysfunction are markers of the diathesis and that DST non-suppression and HPA axis hyperactivity are markers of the acute stress response.

Additionally, reduced cholesterol and BDNF levels in blood serum or plasma may be associated with impaired brain plasticity among individuals with suicidal behavior and ideation. In the future, it will be useful to examine multiple tests and risk factors, including CSF 5-HIAA, DST, cholesterol, and BDNF levels, as well as patient history of attempted suicide, in the prediction of suicide risk, especially among patients with depression.

We propose a model that predicts suicide risk that also considers several factors. We based this model on the Child-Pugh classification system of severity of chronic liver disease (Pugh et al. 1973) and the model is presented in Table 1. Abnormal findings associated with serotonin or HPA activity are more significant among individuals with major depression or with previous histories of attempted suicide (Coryell and Schlessner 2007; Coryell et al. 2006). Additionally, an interaction effect of childhood abuse and gene polymorphisms of serotonin transporters and BDNF has also been reported to influence the risk for suicidal behavior (Currier and Mann 2008). Suicide is associated with dysfunction in the prefrontal cortex, which is related to poor executive function. Such dysfunction can be measured with the

Parameter	Points assigned			
	0	1	2	3
Childhood abuse history	negative		positive	
Current depression	negative	positive		
Previous attempt	0	1		≥ 2
Genetic factors	negative		positive	
CSF 5-HIAA	> cut-off		≤ cut-off	
DST	suppression		Non-suppression	
BDNF levels	normal		decreased	
Cholesterol levels (mg/dl)	≥ 180	180-150	< 150	
Wisconsin Card Sort Test	Normal		Abnormal	

BDNF, brain-derived neurotrophic factor, DST, dexamethasone suppression test, CSF, cerebrospinal fluid, 5-HIAA, 5-hydroxyindoleacetic acid. Our hypothesis is that the total score of these parameters is correlated with current risk of suicide in major depression.

Table 1. Proposed classification of multiple factors to explain risk of suicide in major depression.

Wisconsin Card Sorting Test, and reported deficits in executive functioning are associated with high-lethality suicidal attempts among individuals with major depression (Keilp et al. 2001). Table 1 outlines nine risk factors for suicidal behavior and assigns one point to each factor. It is hypothesized that the total score of these risk factors is correlated with current risk of suicide.

8. Conclusions

Suicide is a complicated phenomenon that results from the interaction of several factors, including neurobiological changes, genetic predisposition, and psychological factors. Postmortem and clinical studies suggest that serotonin dysfunction is a form of diathesis or trait style-risk factor while HPA dysfunction is associated with stress response or state-dependency. Decreased cholesterol and BDNF levels are also related to brain dysfunction among suicidal individuals. Decreased serotonin functioning among suicidal individuals has been measured with CSF 5-HIAA, fenfluramine challenge studies, and levels of platelet 5-HT_{2A} receptors. HPA axis dysfunction has been evaluated using the DST. Cholesterol and BDNF levels can be measured in blood serum or plasma. Additionally, serotonin dysfunction and lower BDNF activity has been found in the prefrontal cortex of the brain in suicidal individuals. Impairment in this region may be associated with behavioral disinhibition and executive dysfunctions, which is often examined with neurocognitive tests. We have proposed a model that incorporates present research on biological factors that may contribute to suicide risk. Clinical studies are needed to evaluate the validity of our risk scale for suicide, but we believe that based on current evidence, this provides a comprehensive screen.

It remains challenging to identify neurobiological predictors of suicidal behavior that are promising and easily assessable. Since suicidal behavior is a complex phenomenon, a multi-dimensional approach, including the above assessments, may be required to predict suicide risk, especially among individuals with major depression. A better understanding of the neurobiology of suicide in major depression will help detect at risk individuals or populations, and help develop better treatment interventions.

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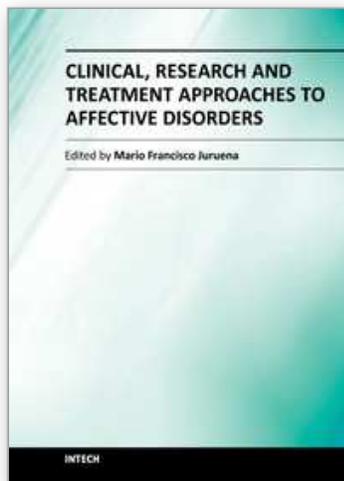
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The causes, development and outcomes of disorders are determined by the relationship of psychological, social and cultural factors with biochemistry and physiology. Biochemistry and physiology are not disconnected and different from the rest of our experiences and life events. This system is based on current studies that report that the brain and its cognitive processes show a fantastic synchronization. Written by the foremost experts on Affective Disorders worldwide, this book is characterized by its innovative, refreshing, and highly sensitive perspective on current knowledge of diagnostic, neurobiology, early life stress and treatment of Mood Disorders. The authors share a deep understanding of unique challenges and difficulties involved in Affective Disorders, and have achieved a balance among clinical, research and new treatment approaches to Affective Disorders. The chapters are written in a comprehensive, easily readable, and highly accessible style, stimulating readers, clinicians and researchers.

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