Review

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# Neurobiological Basis of Violence and Suicide in Alcohol/Substance Use Disorders

## *Alkol/Madde Kullanım Bozukluklarında Şiddet ve İntiharın Nörobiyolojik Temelleri*

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**ABSTRACT**

Both the risk of suicidal and violent behaviours increases in alcohol and substance use disorders. Besides, it's proposed that alcohol and substance use disorders significantly contribute to the increasing prevalence of suicide and violence worldwide. For these reasons, it is thought that the spiral of problems consisting of the concepts of suicide, violence, and addiction awaits a solution on a global scale. The discovery of the underlying neurobiological mechanisms is required to deal with these problems. Previous research has revealed the importance of neurobiological mechanisms in understanding suicidal, violent, and addictive behaviours. Especially recent studies have shown some evidence that these three conditions have some related genetic, epigenetic, and neurobiological bases. Therefore, besides the current neurobiological research on alcohol and substance use disorders, scientific literature related to suicidal and violent behaviours will be presented in this review altogether.

**Keywords:** Substance-related disorders, alcoholism, violence, suicide, psychiatry

**ÖZ**

Alkol ve madde kullanım bozukluklarında hem intihar davranışı riski hem de şiddet davranışı riski artmaktadır. Ayrıca, alkol ve madde kullanım bozukluklarının dünya genelinde artan intihar ve şiddet yaygınlığına önemli ölçüde katkıda bulunduğu ileri sürülmektedir. Bu nedenlerle intihar, şiddet ve bağımlılık kavramlarından oluşan sorunlar sarmalının küresel ölçekte çözüm beklediği düşünülmektedir. Bu problemlerle başa çıkmak için altta yatan nörobiyolojik mekanizmaların keşfi gereklidir. İntihar, şiddet ve bağımlılık davranışlarını anlamada nörobiyolojik mekanizmaların önemi daha önceki araştırmalarda ortaya konulmuştur. Özellikle son zamanlarda yapılan çalışmalar, bu üç durumun birbiriyle ilişkili genetik, epigenetik ve nörobiyolojik temellere sahip olabileceğine dair bazı kanıtlar göstermiştir. Bu nedenle bu derlemede alkol ve madde kullanım bozuklukları ile ilgili güncel nörobiyolojik araştırmaların yanı sıra intihar ve şiddet davranışları ile ilgili bilimsel yazın bir arada sunulacaktır.

**Anahtar sözcükler:** Madde kullanımına bağlı bozukluklar, alkolizm, şiddet, intihar, psikiyatri

## Introduction

The World Health Organization (WHO) defines the violence as "the intentional use of physical force or power, threatened or actual, against oneself, against another person or against a group or community, which either results in or has a high likelihood of resulting in injury, death, psychological harm, mal-development, or deprivation" (Krug, Mercy et al. 2002). The WHO divides violence into three categories: self-directed, interpersonal, and collective **(Table 1)**. The violent behavior in mental disorders is quite complex (Jacobs et al. 2010, Krug et al. 2014). When considering violent behavior in mental disorders, the first thing that leaps to mind is violence occurring in interpersonal relationships. In this case, the family and close circle of people with mental disorders are viewed as the primary victims of violence. However, this approach is deficient because violence is a vicious circle in mental disorders. The crucial point is that the other violence type as classified by WHO is that self-directed violence (Ercan et al. 2000). The most basic form of self-directed violence in patients with mental disorders is suicide. Suicide is more prevalent in those with mental disorders than in the general population. Suicide rates differ according to the type of mental disorders. A previous study reported that the lifetime risk of suicide was 20 times higher for major depression, 15 times for

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bipolar affective disorder, 12 times for dysthymia, 8 times for schizophrenia, 11 times for obsessive-compulsive disorder, and 10 times for panic disorder (Jacobs, Baldessarini et al. 2010). When we look at the whole picture regarding all violence types, it is observed that self-directed and interpersonal violent behaviors increase in mental disorders.

Another topic when investigating the underlying causes of mental problems, people with mental disorders have a more prevalent childhood trauma history (Bakar Kahraman ve Kızılay Çankaya 2020). Besides, stigmatization for having a mental disorder is another form of violence experienced by these individuals. Stigmatization towards mentally ill people cause the mental disorder to deepen and have a poorer prognosis (Cam and Bilge 2013). From this point of view, it seems that society paves the way for violent behaviors. Therefore, there is a complex and ongoing relationship between violence and mental disorders. This relationship is summarized in **Table 2**. The prevalence of suicide, violence, and addiction has been becoming increasingly common and awaiting a solution on a global scale. Besides the psychosocial interventions, underlying neurobiological mechanisms need to be addressed. Research in this area has revealed the importance of neurobiological mechanisms in understanding suicide, violence, and addictive behaviors (Arseneault et al. 2000, van Heeringen ve Mann 2014, Koob ve Volkow 2016). Recent studies, in particular, have shown strong evidence that these three conditions may have some associated genetic, epigenetic, and neurobiological underpinnings (Lutz et al. 2018, Cheung et al. 2020). Therefore, in this review, current neurobiological research on alcohol and substance use disorders and scientific literature on suicide and violent behaviors will be presented together. In the light of our literature review, we think that a holistic approach to the findings of different but related pathologies would be beneficial in understanding these problems and guiding the literature search.

## Neurobiological Mechanisms in Violent Behavior

Many neurobiological mechanisms have been proposed in the pathophysiology of violent behavior. According to the current scientific knowledge, it is not precisely known which factors how much affect violent behavior. However, one can draw a general framework of these factors based on the existing literature.

**Genetics** has been perhaps the most investigated area in the pathophysiology of violent behavior. Previous studies suggest that the effect of genetic characteristics on violent behavior varies according to age. According to that, while the effects of genetics and environment are similar in youth, the impact of genetic factors increases with age (Craig and Halton 2009). In twin studies, it has been reported that the effect of genetic structure on violent behavior can be as much as 60% to 79% (Blonigen and Krueger 2005). Previous genetic studies suggested some genetic variations in the pathophysiology of violent behavior: the p11-p21 region of the X chromosome (monoamine oxidase type A and B receptor-related), catechol O-methyl transferase (COMT) enzyme polymorphism in 22q chromosome, defects in dopamine beta-hydroxylase and tryptophan hydroxylase enzymes, and neuroepithelial cell transformation 1 (Blonigen and Krueger 2005).

**Neurotransmitters** have been investigated in the pathophysiology of violent behavior. Serotonin and dopamine are the neurotransmitters on which most studies have been conducted. Decreased serotoninergic activity in the prefrontal cortex and anterior cingulate cortex is directly related to aggression (Sopromadze and Tsiskaridze). One study revealed increased serotonin metabolite (5-hydroxyindolacetic acid) in the cerebrospinal fluid (CSF) of aggressive patients (van Praag, Asnis et al. 1990). Besides, it was reported that an increase in the amount of dopamine in the mesolimbic pathways was closely related to aggressive behaviors (Depue and Spoont 1986).

Neuroimaging studies have been very helpful in clarifying many theories on violent behavior. However, the results have been difficult to interpret due to neuronal structures whose function is not yet understood and the limitations of the studies. A significant number of studies revealed that there was a clear relationship between dysfunction in the frontal lobe and violent behavior. Previous studies demonstrated that executive functions such as impaired emotional responses, impaired judgment, increased impulsivity, and decreased self-control occur due to dysfunctions of the orbitofrontal cortex, dorsolateral cortex, and anterior cingulate cortex (Phelps 2006, Pardini, Raine et al. 2014). The amygdala and nucleus accumbens were other neuronal structures found to be associated with violent behavior. The amygdala is mainly responsible for regulating fear response, and its basolateral nucleus plays an important role in the conscious response to a stimulus, associating the emotional response with memory and strengthening the autonomic nervous system's response. It was reported that there was a relationship between the size of the amygdala, especially the right amygdala, and aggression (Pardini, Raine et al. 2014). The fact that violent behavior is more common in men and the size of the amygdala is larger than that of women supports the result of this study. The nucleus accumbens has an important role in the regulation of behavior because it receives significant input from the amygdala and is closely related to the orbitofrontal cortex (Phelps 2006).

## Neurobiological Mechanisms in Suicidal Behavior

One person dies by suicide every 40 seconds in the world. Suicide is a leading cause of death and a major global health problem. It is estimated that 800,000 people die by suicide each year and there are 25 million non-fatal suicide attempts per year (O'Connor, Gartland et al. 2020). Although the suicide rate is high in people with psychiatric disorders, a significant portion of patients doesn't exhibit suicidal behavior. Therefore, it is thought that there is a general predisposition for the formation of suicidal behavior. According to the stress-diathesis model, suicide cases occur as a result of the interaction of environmental factors with individual susceptibility (Broerman 2017). This model provides an opportunity to integrate neurobiological

phenotypes with clinical and cognitive perspectives while investigating suicidal behavior.

Studies in the field of genetics have revealed that suicide has a genetic basis. Interestingly, heredity is estimated to contribute 43 percent to suicide attempts (McGuffin, Perroud et al. 2010). Studies showing that suicide has a genetic basis rely on family, adoption, and twin studies (Özalp 2009). Family studies have shown that suicide rates are higher in relatives of individuals who commit suicide. These higher rates continues even when the effect of psychopathology is controlled (Aydın, Hacımusalar et al. 2019). Findings from a small number of adoption studies have shown that the biological relatives of suicidal individuals have a higher risk of suicide. In a rare study conducted in Denmark, where the patient registration system is highly developed, 5483 adoption records were examined. Among these, it was reported that there were 57 completed suicides and when these cases were compared with the adopted controls, 12 of 269 biological relatives of these 57 suicide cases died by suicide. On the other hand, this figure was only two for the relatives of the people in the control group. According to this study, the suicide rate in the biological relatives of those who died by suicide was six times higher than in the control group (Yüksel 2001). Twin studies have shown a higher risk of suicide in monozygotic twins than dizygotic twins and a higher risk of suicide in dizygotic twins than in the general population (Brent and Mann 2005). In addition, it was reported that there were some intermediate phenotypes in the transmission of suicidal behavior. These are impulsive aggression, neuroticism, and neurocognitive disorders that are thought to be inherited (Brent and Melhem 2008).

Considering the first studies at the gene level, it has been suggested that polymorphisms of some genes are associated with suicidal behaviors. Some of these are serotonin transporter receptor (SERT), tryptophan hydroxylase (TPH), some serotonin receptors (5HT1A, 5HT1B, 5HT2A), catechol-O-methyltransferase (COMT), monoamine oxidase A (MAOA), tyrosine hydroxylase (TH) genes (Özalp 2009). As a result of understanding the importance of epigenetic mechanisms in the following years, changes that affect gene expressions such as micro-RNA (miRNA) interference, DNA methylation, and histone modification have been emphasized to understand better the gene-environment interaction at the molecular level (Cheung et al. 2020).

There is a range of studies suggesting that the noradrenergic system is associated with suicidal behavior. In one of these studies, in postmortem examinations of the brains of people who died as a result of suicide, there was a decreased number and density of pigmented neurons in the locus ceruleus, where noradrenergic neurons are most concentrated, compared to controls (Arango, et al. 1996). The blood and urine levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), the main metabolite of norepinephrine, were found to be lower in people who attempted suicide compared to controls (Secunda et al. 1986). In rodents and possibly humans, distress experienced in the early stages of life has been shown to increase the organism's susceptibility to norepinephrine secretion to stressors (Heim and Nemeroff 2001). It was proposed that the decreased number of noradrenergic neurons and the increased sensitivity of the norepinephrine response to stress factors possibly lead to depletion of norepinephrine in noradrenergic neurons and thus reduced MHPG concentrations in the central nervous system and peripheral (van Heeringen and Mann 2014). Studies evaluating receptor density stated that people with suicidal behavior have an increase in beta and a2 adrenergic receptor density in the frontal cortex (Aydın et al. 2019). It was suggested that the increased adrenergic receptor density in the frontal cortex as well as the increased activity of tyrosine hydroxylase, the rate-limiting enzyme of catecholamine synthesis, occur as a response to norepinephrine depletion (Mann 2003).

The studies investigating the role of the dopaminergic system on suicidal behavior include the changes in dopamine metabolites, dysfunction in dopamine receptors, and hormone stimulation studies. Homovanillic acid is the major metabolite of dopamine, and homovanillic acid levels in the central and, to a lesser extent, peripheral, are an important indicator of dopamine metabolism (Amin et al. 1992). It was reported that there was no definite relationship between homovanillic acid levels in the cerebrospinal fluid and suicidal behavior (Jokinen et al. 2009). According to a hormone stimulation study, the peak growth hormone response to apomorphine, a dopamine agonist, is significantly lower in depressed patients with suicidal behavior compared to those without suicidal behavior (Pitchot et al. 2001). Since this study measured a dopaminergic response at the level of the hypothalamus, the study does not provide information about the mesocortical and mesolimbic pathways. In a recent postmortem study, patients with depression who died as a result of suicide and those who died due to non-suicidal reasons were compared in terms of dopamine receptor binding profiles (Fitzgerald et al. 2017). The authors reported that there was no significant difference between the two groups in terms of radioligand binding rates to D1 receptor, D2 receptor and dopamine transporter, but there was no correlation between D1 and D2 receptor binding rates in people who died by suicide, unlike the control group. These results have been interpreted as non-depressed people can regulate the relative expression levels of these two types of dopamine receptors, but depressed people with suicidal behavior may not do this effectively. However, it is unknown whether this difference is due to depression or previous psychotropic drugs used by the patients.

It has been shown that there are disorders related to the functioning of the hypothalamus-pituitary-adrenal (HPA) axis, which has a critical role in the stress response in suicidal behavior. (O'Connor et al. 2016). Epigenetic differences in the expression of the NR3C1 gene, which is responsible for the expression of the glucocorticoid receptor (GR), have been found to be associated with suicide (McGowan and Szyf 2010).

The neurotrophic system is a family of growth factor proteins that support the development, differentiation, function, plasticity, and survival of the neuronal cells (Oliveira et al.

2013). Among those, serum levels of brain-derived neurotrophic factor (BDNF) have been shown to be closely associated with the course of schizophrenia and mood disorders. (Peng et al. 2018). The Val66Met polymorphism of the BDNF gene responsible for BDNF production has been shown to be associated with reduced hippocampal BDNF activity and secretion (Chiaruttini et al. 2009). According to epigenetic studies, BDNF promoter CpG methylation is associated with decreased neuronal BDNF synthesis (Martinowich et al. 2003) and suicide (Keller et al. 2010). There is some evidence that traumas experienced in the early stages of life lead to methylation of the BDNF gene, which leads to neuropsychiatric disorders such as depression, schizophrenia, bipolar disorder, and autism (Kundakovic et al. 2015).

Studies linking suicide with serotonergic activity or candidate genes have produced mixed results (Buttenschøn et al. 2013). For example, according to the epigenetic studies on the 5HT2A receptor gene, which is one of the serotonergic genes that may be associated with suicide, and the tryptophan hydroxylase 2 (TPH2) gene, which is involved in the synthesis of serotonin in neurons, hypermethylation of the promoter regions of these genes is associated with suicide. In contrast, there are findings that claim the opposite in some other studies. (Cheung et al. 2020).

Considering the epigenetic mechanisms of suicide, the most promising findings in understanding the neurobiology of suicide have been obtained from studies investigating the relationship between BDNF gene modification and suicide. Studies on microRNA and histone modification are also ongoing. The findings have not shown a robust relationship so far (Cheung et al. 2020).

The findings from neuroimaging studies indicate that the orbitofrontal cortex, dorsolateral prefrontal cortex, insula, superior temporal gyrus, basal ganglions (caudate nucleus and globus pallidus) have diminished gray matter volume (mainly in the right hemisphere) in those with a suicide attempt (van Heeringen et al. 2011). In contrast, the thalamus and right amygdala volumes are higher in those who attempt suicide. Findings of white matter hyperintensities (especially periventricular), increased bilateral volumes of the inferior frontal white matter tracts (especially in the uncinate fascicle and inferior orbitofrontal fascicle), and lower anisotropy in the left orbitofrontal area and the left forearm of the inner capsule indicate structural connectivity disorders associated with suicidal behavior (van Heeringen et al. 2011). Functional neuroimaging findings associated with suicidal behavior mainly include altered reactivity to various stimuli noted in the bilateral orbitofrontal, right ventromedial and anterior cingulate, and left dorsolateral prefrontal cortex areas. Functional connectivity between the anterior cingulate and posterior insula is decreased and connectivity increased in the striatal motor-sensory network in those with suicide attempt (van Heeringen and Mann 2014).

## Neurobiology in Substance Use Disorders

Drugs cause irreversible damage to the brain. After the detection of these damages in neurobiology-based imaging studies, the perspective on substance use disorders changed. (Koob and Volkow 2010). After studies in the field of neurobiology, substance use disorders began to be considered as a brain disease or brain disorder.

The most accepted neurobiological cycle related to alcohol/substance use disorder was presented by Koob and Volkow (2010). There are three stages in this cycle;

1. Binge/intoxication stage
2. Withdrawal/negative affect stage
3. Preoccupation/anticipation (craving) stage

### Binge/Intoxication Stage

After substance intake, the various receptors in the ventral tegmental area are stimulated, depending on the substance ingested. After this stimulation, there is a sudden and high release of dopamine in the nucleus accumbens (Hernandez et al. 2006). The dopamine release after substance intake causes a different perception of pleasure and enjoyment compared to derived from natural rewards (Koob and Volkow 2010). Because dopamine release after natural rewards (reading a book, watching a movie, walking, eating, etc.) occur in a longer time and is less in amount. After dopamine release, the pathways from the nucleus accumbens to the dorsal striatum are activated (Nestler 2005). The dorsal striatum is a crucial center from the transition of feeling pleasure to habit. The Striatum-Globus Pallidal-Thalamus-Cortex network is the pathway through where the habit is formed and controlled. (Everitt et al. 2008).

### Withdrawal/Negative Affect Stage

After intense substance use, the brain enters an adaptation process. It creates an anti-reward system despite increased reward pathways. (Koob and Volkow 2016). The main goal of creating this anti-reward response is to reduce damage to the brain. At this stage, dopamine and serotonin decrease in the nucleus accumbens, the hypothalamo-pituitary-adrenal axis is activated, and CRF increases in the amygdala. There is an increase in mu-opioid receptor response (due to a decrease in opioidergic substrates). Also, GABA decrease and a glutamate increase are observed in the nucleus accumbens (Melis et al. 2005, Koob and Volkow 2016). These changes reduce the level of pleasure created by the substance taken. Because the brain has activated the anti-reward system with neuroadaptation. Decreased pleasure over time causes negative emotions in the individual (Koob and Kreek 2007). When substance withdrawal is superimposed on these negative feelings, the individuals' emotional state further worsens. Studies show that the pleasurable feature of the substance decreases significantly during this period. These properties may partly explain why addicted individuals also lose interest in natural rewarding actions (Koob and Simon 2009, Koob and Volkow 2010, Koob and Volkow 2016).

### Preoccupation/Anticipation (Craving) Stage

The deprived individual who lacks pleasure thinks that he can overcome this situation by increasing the amount of the

substance he uses, so the addiction becomes more severe. The repetitive substance use causes the so-called neutral objects or situations to turn into triggers. For example, a friend who has been using drugs together for a long time become a trigger for the drug user. Whether this friend uses drugs or not, the desire to buy drugs arises when the individual sees this friend. Another example is when a song is listened to during substance use; even if the individual has stopped using the substance, a desire for substance use occurs when the song is played. One of the important centers of processing these conditioned reinforcers is the basolateral amygdala (Schulteis et al. 2000). Besides this neuronal structure, the hippocampus is another important center in the processing of contextual information. The prefrontal cortex and the glutamatergic pathways between these two structures regulate behavior when substance-related stimuli occur (Koob and Volkow 2010). In addition, the prefrontal cortex controls the stimulation of dopaminergic neurons in the ventral tegmental area. This pathway is regulated by glutamatergic neurotransmission (Koob and Volkow 2016). An increase in the desire for substance use does not always lead to substance reuse. If the individual also has impairments in the GABAergic activation in the prefrontal system, the risk of substance reuse increases significantly. The executive dysfunction (decision-making disorder, lack of self-control, and working memory impairments) emerge due to prefrontal cortex damage. The individual tends excessively to stimuli associated with the substance, his response to non-substance-related rewards decreases, and he experiences difficulty in suppressing maladaptive behaviors (Bolla et al. 2003, Aharonovich et al. 2006).

The reduced self-control due to impaired prefrontal cortex functions in substance users increases the risk of violent behaviors. The most basic mechanism in the occurrence of violence in substance use disorders is the deterioration in prefrontal cortex functions.

## Psychiatric Disorders and Violence

Lindqvist and Allebeck (1990) examined the violent crime rates of patients with schizophrenia and society. They stated that the crime rates of the patients were four times higher than the general population and almost all of these crimes were minor. Volavka et al. (1997) in their study, in which they examined 1017 schizophrenia patients participating from ten countries, found the frequency of violent behavior to be 20.6%. However, the rates of violent behavior were higher in those from underdeveloped countries, those with auditory hallucinations, and those with accompanying alcohol use problems. In the criminal-based study of Gray et al. (2011), 996 patients who were discharged from the psychiatric ward between 1992 and 2000 were followed up for violent crime for two years. In the two-year follow-up period, the violent crime rates were 19.4% for all psychiatric diseases, 19% for mood disorders, and 15.6% for schizophrenia. The prevalence of violent behavior in bipolar mood disorder was similar to that of schizophrenia. Violent behavior increases especially in mania and mixed periods. In addition, one of the main diagnostic criteria of these periods of bipolar mood disorder is increased irritability (APA 2013). In depression, aggression is a behavior directed towards oneself from a psychoanalytic point of view. Suicide may occur as a result of self-directed aggression (Özer et al. 2015). A study evaluating the frequency of violent behaviors in an epidemiological design reported that the rate of violent behavior was 16% for those with bipolar disorder, 9.1% for those with alcohol abuse, 19.8% for those with substance abuse, and 2% for those without any disease (Corrigan ve Watson 2005). A previous study evaluated the lifetime prevalence of violent behaviors among 43093 adults in the United States (Pulay et al. 2008). In this study, while the frequency of violent behavior was 0.6% in patients without psychiatric disorders, these rates were found to be 25.3% and 13.5% in type 1 and type 2 bipolar mood disorders, respectively. Based on these data, violence in mental disorders can be viewed from two perspectives. The first of these is violence caused by the mental disorder without alcohol/substance use disorder. The second is violence that worsens when a mental illness is accompanied by alcohol/substance use disorder. In other words, alcohol/substance use disorders can increase self-directed and interpersonal violence in people with mental disorders.

Studies investigating the relationship between psychiatric disorders and violence have identified many risk factors for violent behavior. These include male gender, being in the young age group, presence of violent behavior in family history, presence of childhood trauma, poor socioeconomic status, presence of negative life events more frequently, presence of personality disorder, non-adherence to treatment, early onset of addiction, presence of violent behavior in the past, presence of suicide attempt (Eronen et al. 1996, Steinert et al. 1999, Arseneault et al. 2000, Quanbeck et al. 2005, Garno et al. 2008, Fazel et al. 2009). In addition to these factors, the presence of alcohol/substance use disorder significantly increases violent behavior.

## Psychiatric Disorders with Comorbid Alcohol/Substance Use Disorders And Violence

Torrey (1994) compared those with and without mental disorders in terms of violent behavior. He stated that those with mental disorders did not differ significantly from the general population in terms of displaying violent behavior, but a small subgroup was found risky for violent behavior. That subgroup had previous violent behavior, non-compliance with drug treatment, and had a substance use disorder. Arseneault et al. (2000) reported that violent behavior increased 1.9 times in those with alcohol dependence and 3.8 times in those with marijuana addiction. However, the authors emphasized that although these disorders constituted one-fifth of the study sample, they constituted about half of the crimes committed (Arseneault, Moffitt et al. 2000). In their meta-analysis, Fazel et al. (2009) concluded that people with psychotic disorders exhibited more violent behavior than the general population. They also denoted that the frequency of violent behaviors significantly increased with substance use disorders in these patients. Steinert et al. (1999) investigated both the frequency of interpersonal and self-directed violence in patients with schizophrenia. 75% of the males and 56% of

the females in the sample adopted an aggressive attitude. 17% of men and 26% of women had a history of suicide attempt. Factors associated with aggressive behavior were male gender, rehospitalizations, and alcohol use disorder. Murder cases and the perpetrators of repetitive homicide cases were investigated over 13 years by Eronen et al. (1996). They reported that 75% of the perpetrators of repetitive murder cases had alcohol use disorder (Eronen et al. 1996). Çinik et al. (2015) compared violent behavior rates according to the presence and absence of substance use disorder in schizophrenic patients. In the comorbid schizophrenia and substance use group the number of crimes was higher, and serious violent behavior, and exposure to physical violence in childhood were more frequent. They also stated that 88% of the comorbid group reported that they were under the influence of the substance when they committed the crime.

Bipolar disorder is the most common mental disorder accompanied by alcohol/substance use disorders. The accompanying alcohol/substance use disorder increases the frequency of violent behavior as in other mental disorders. Garno et al. (2008) investigated the causes of aggression in bipolar mood disorder. One of the important variables was identified as substance use disorder. However, violent behavior was found to be closely related to the severity of the disease (Garno et al. 2008). Quanbeck et al. (2005) investigated the reasons for arrest in those with bipolar affective disorder. In this study, while 76% of the arrested patients were found to have a substance use disorder, 19% of those who were not arrested had a substance use disorder(Quanbeck, Stone et al. 2005)(Quanbeck, Stone et al. 2005)(Quanbeck, Stone et al. 2005)(Quanbeck, Stone et al. 2005)(Quanbeck, Stone et al. 2005) (Quanbeck, Stone et al. 2005) Sublette et al. (2009) investigated the relationship between substance use disorder and suicide in bipolar affective disorder. Presence of substance use disorder was found to be associated with Type 1 bipolar mood disorder, but not with Type 2 bipolar disorder. They found that individuals with type 1 bipolar affective disorder have higher aggression scores in those who have attempted suicide related to alcohol use disorder. Besides, they concluded that substance use disorder in those with type 1 bipolar affective disorder increased the risk of suicide attempts by increasing impulsivity, hostility, and aggression. In this patient group, the presence of alcohol use increased the risk of suicide 5 times, while the presence of substance use disorder increased the risk of suicide 11 times. The relationship between violent behavior and substance use includes a process in which one causes the other. A similar relationship is valid for violent behavior and personality disorders (Geniş and Coşar 2018). Stoffel et al. (2019) investigated traumatic experiences in crack users with and without antisocial personality disorder (ASPD). In both groups, the rate of physical violence by a known person was found to be quite high (59% and 46%, respectively). However, in the same study, the case of committing a violent crime in groups was also investigated. While the rate of committing a violent crime is 53.5% in crack users with ASPD, this rate is 37.5% in non-ASPD crack users. The results of this study show that people with ASPD are exposed to more violence and use more violence. Intermittent explosive disorder (IED) is one of the psychiatric disorders often accompanied by violent behavior and alcohol use disorder. IED is an important psychiatric disorder in which aggression appears as the main symptom. Although this disorder is thought to be rare, its prevalence is approximately 5% in the community. Puhalla et al. (2020) compared the patients with IED and the healthy control group in terms of comorbid psychiatric disorders and some characteristics. According to the results substance use disorder and personality disorders were significantly higher in those with IED diagnosis than in the control group. One of the important results of the study is that the probability of developing IED increases 11.2 times in those with a diagnosis of personality disorder, 4 times in those with childhood trauma, and 3.8 times in people with alcohol use disorder. This study also reveals that there are important links between violence experienced in childhood and violence in adulthood.

## Alcohol/Substance Use Disorders and Violence

Alcohol and substance use disorders also affect the social structure in terms of violent behavior, loss in the workforce, adversely affecting family members, and transferring genetic addictions. Alcohol/substance use disorders lead to violent behaviors by deteriorating executive functions, self-control, and decision-making. The patient, their relatives and the society suffer serious damage from this violence. Interestingly victims of violence use alcohol or drugs to reduce the impact of their trauma. Previous studies have shown that the perpetrators had consumed alcohol or other substances before committing the crime. From this point of view, alcohol or substance is used both as a trigger of violence and as a wrong coping strategy to reduce the mental distress caused by violence. This situation is a concrete indication of the spiral of problems in alcohol or substance use disorders. In alcohol or substance use disorders, violence can occur during abstinence and intoxication. However, there may be many other factors associated with violent behavior. The type of substance, frequency of use, duration of use and route of administration are some of them. Swanson et al. (1990) investigated the relationship between psychiatric disorders and violent behavior. The authors reported that substance use disorder had the strongest relationship with violent behavior among psychiatric disorders. The authors also stated that patients with alcohol/substance use disorder have twice the risk of violent behavior compared to patients with schizophrenia. (Swanson et al. 1990).

Roy (2009) investigated the frequency of suicide (as a result of self-directed violence) and related factors in patients with cocaine addiction. In this study, it was reported that 43% of the patients attempted suicide at least once. Factors such as childhood trauma, accompanying alcohol/opioid use disorder, and a family history of suicide attempt were found to be associated with suicide attempt. Mantalvo et al. (2012) investigated the frequency of violent behavior in those with substance use disorders. They found that 40% of the participants exhibited violent behavior. Those with violent behavior were at a younger age and they were frequent substance users. However, one out of every two individuals with violent behavior had a history of abuse. A considerable part of the studies in the literature includes violent behavior of people

with alcohol/substance use disorder. Marshall et al. (2008) investigated the frequency of exposed violence in patients with substance use disorders. The researchers, who followed the patients for five years, found that 66% of the women and 70% of the men were exposed to violence at least once during these five years. Being homeless, having frequent alcohol/substance use, and having a severe mental disorder significantly increased the risk of exposure to violence. In Turkey, Türkmen and Epsoylu (2019) investigated the crime involvement and related variables in an addiction center. It was determined that 34% of the sample in the clinic had committed a crime. The authors stated that 71% of the patients who committed crimes were exposed to violence in their childhood and 95% of them had a relative who had committed a crime (Turkmen and Epsoylu 2019). Inandı et al. (2009) investigated the frequency of substance use and its relationship with violence in high school students. As a result of this study, it was determined that students who use cigarettes or other substances have higher rates of being exposed violence and committing violence in the last year.

## Alcohol and Substance Use Disorders and Suicide

While all substances increase the risk of suicidal behavior, alcohol (22%) and opioids (20%) are the most common substances detected in people who died by suicide (Esang and Ahmed 2018). These rates are well above the rates of cannabis (10.2%), cocaine (4.6%) and amphetamine (3.4%) (Esang and Ahmed 2018). According to the findings obtained from a meta-analysis, acute alcohol intake was associated with a 7-fold increased risk of suicide attempt (Borges et al. 2017). In addition, the higher the amount of alcohol consumed, the higher the risk of suicide attempt was determined. While there is a risk of suicide three times after a small amount of alcohol intake, this rate increases up to 37 times with high amounts of alcohol intake (Borges et al. 2017). It was proposed that acute effects may occur in acute alcohol consumption through suicidal ideation, dysphoria, disinhibition, impulsivity, myopia, and increased intensity of aggression. On the other hand, the effects of regular heavy alcohol use on suicide risk may arise from the interrelationships between depression and alcohol use (Pompili et al. 2010, Bagge et al. 2014). Alcohol use disorders are highly associated with Axis I and Axis II psychiatric pathologies and adversely affect their course (Castillo-Carniglia et al. 2019). According to a meta-analysis, lifetime prevalence of alcohol use disorder was 77% in people with antisocial personality disorder, 52% in people with borderline personality disorder, and 39% in people with other personality disorders (including combined or undifferentiated personality) (Guy et al. 2018). The lifetime prevalence of alcohol use disorder among those with lifelong major depression ranges from approximately 27% to 40% in epidemiological studies in the USA (Sullivan et al. 2005). Multinational studies indicate that there is a linear relationship between suicide rates and per capita alcohol consumption (Ramstedt 2001). There has been an increase in both alcohol intake and suicide rates in the past 20 years (Shiels et al. 2020). It was reported that the prevalence of high-risk drinking has increased by 29.9% and alcohol use disorder by 49.4% in the USA since 2001 (Grant, Chou et al. 2017). Besides, it was found that there was a 35% increase in alcohol-related suicidal deaths (Hedegaard, Curtin et al. 2020). Considering that the relationship between alcohol intake and suicide is not causal, both behaviors aim to avoid a negative emotional state. Thus, it can be thought that alcohol is a facilitating mediator that increases the risk of suicide as a result of paradoxically increasing dysphoria.

Alcohol use disorder and suicide attempt share some common neurobiological features. According to a postmortem study, it was reported that there was a localized increase in 5-HT1A binding in the ventral prefrontal cortex in non-alcoholic suicides, but this increase was not observed in alcoholic suicides. For this reason, it has been reported that upregulation of ventral prefrontal

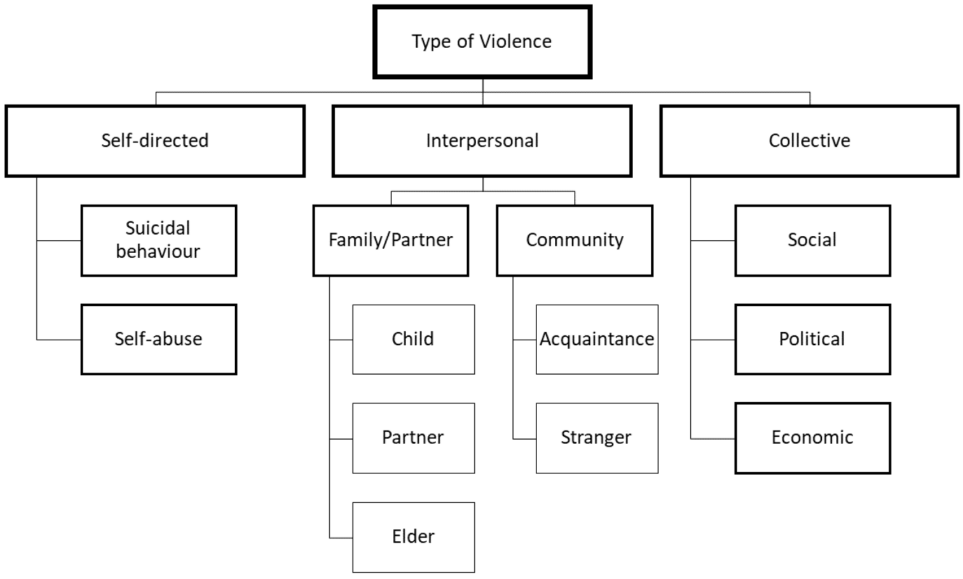


**Figure 1.** The World Health Organization's classification of types of violence

5-HT1A receptors cannot be achieved in response to decreased serotonergic transmission in alcoholic suicides, and that less serotonin may not alleviate the effect on signal transmission, thus increasing the risk of suicidal behavior (Underwood et al. 2004). It has been shown that the level of 5-hydroxyindolacetic acid (5-HIAA), a serotonin metabolite, is decreased in the cerebrospinal fluids of alcohol-dependent individuals, and this indicates a decrease in serotonergic transmission (Placidi et al. 2001). In addition, the S allele of SLC6A4, a serotonin transporter protein gene, was found more frequently in patients with severe alcohol dependence compared to controls (Sander et al. 1997). Interestingly, a polymorphism in the promoter region of the SLC6A4 gene called 5-HTTLPR was found to be associated with suicidal behavior (Gorwood et al. 2000).

Neuroimaging studies indicate that there are some similar morphological changes in individuals with alcohol use disorder and in individuals with a history of suicide. It has been shown that gray matter volume decreases in the dorsolateral prefrontal cortex of alcoholic and suicidal patients, which has a very important role in decision-making and behavioral inhibition (Wagner et al. 2012, Welch et al. 2013). Diffusion tensor imaging studies show lower white matter integrity in the frontal and limbic regions in both suicide attempters and youths with alcohol use disorder (Rizk et al. 2021). These changes in white matter can be attributed to the neurotoxic effects of alcohol.

It has been known that there are deteriorations in the HPA axis which is an important component in providing a stress response in individuals with a suicide attempt and alcohol use disorder (Rizk et al. 2021). Interestingly, it was observed that individuals with high levels of impulsivity and tendency to violence but exhibiting suicidal behavior showed higher cortisol response to social stressors created in the laboratory environment compared to individuals with low levels of impulsivity and tendency to violence (Stanley et al. 2019).

Macroscopic and microscopic changes in the brain due to neurotoxic effects in individuals with alcohol use disorder make the already problematic system in individuals prone to suicide even more problematic. Therefore, it can be said that acute or chronic alcohol use in an individual genetically predisposed to suicide gives a neurobiological acceleration in the emergence of suicidal behavior.

The relationship between opiate use disorder and increased risk of suicide can be attributed to several factors. Social and environmental disadvantages such as low family support, unemployment, and homelessness are common among those with opiate use disorder and suicidal propensity (Phillips et al. 2004, Roy 2010). Childhood trauma (e.g., physical or sexual abuse) is a crucial early risk factor for suicide and is very common in those with opiate use disorder. (Sansone et al. 2009, Zatti et al. 2017). A history of childhood abuse significantly increases the risk of suicidal behavior in individuals with opiate use disorder (Roy 2002). In addition, it has been reported that 75 percent of individuals with opiate use disorder have at least one accompanying psychiatric disorder, mainly depression and anxiety disorder (Brienza et al. 2000, Cacciola et al. 2001).

In the postmortem brains of chronic opiate users, striatal levels of serotonin were slightly elevated, while levels of the serotonin metabolite 5-hydroxyindolacetic acid were significantly reduced compared to controls (Kish et al. 2001). This suggests that long-term heroin use causes a decrease in serotonin activity (Cosgrove et al. 2010).

In recent years, it has been suggested that kappa opioid receptors are associated with negative affect in people with opiate use disorder. Animal studies suggest that an activated kappa receptor system is an important mediator of dysphoria-related symptoms and depressive behaviors. The expression of kappa receptors are increased in the brains of people who died as a result of suicide (Hurd et al. 1997). In one study, the presence of kappa

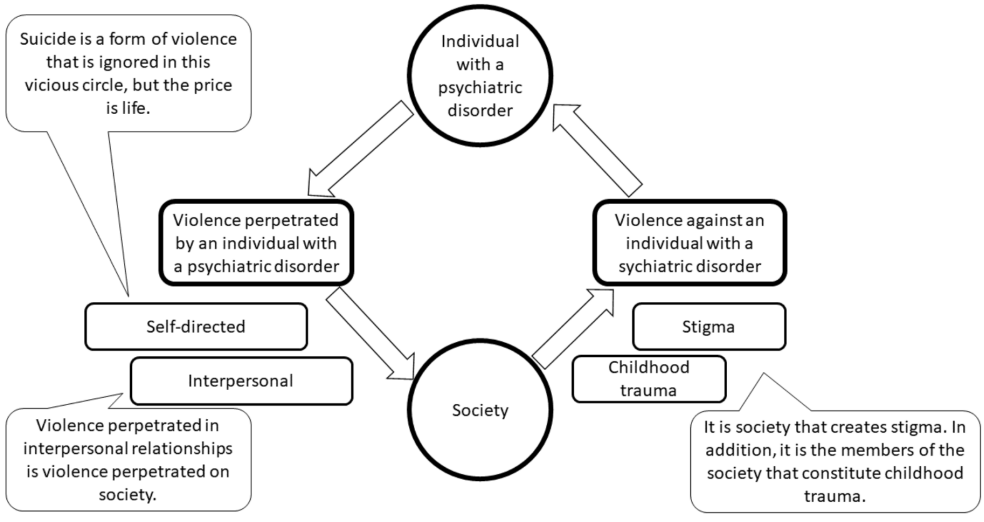


**Figure 2.** The vicious cycle of violence in the relationship between the individual and society

receptors in the amygdala-anterior cingulate-striatal circuit was shown to mediate the expression of dysphoria (Pietrzak et al. 2014). Furthermore, it was reported that some epigenetic modifications related to Kappa receptors are associated with childhood traumas (Lutz et al. 2018).

As a result of the changes in neural connectivity due to chronic opiate use, there is a decreased sensitivity to natural rewards as well as increased sensitivity to negative emotions, stress, and pain in the addicted individuals (Shurman et al. 2010). Both acute and chronic opioid use have been shown to have negative consequences for attention, concentration, recall, visuospatial skills, and psychomotor speed (Gruber et al. 2007). The long-term effects of opiate use appear to have the greatest impact on executive functions, including cognitive restructuring and the ability to inhibit inappropriate response tendencies (Gruber et al. 2007, Fu et al. 2008). Neuroimaging findings and clinical implications have provided convincing evidence that opiate use disorder affects the prefrontal cortex (PFC), insula, thalamus, and nucleus accumbens (amygdala and sensorimotor cortices) (Ieong and Yuan 2017).

In general, when the literature data is examined, a satisfactory neurobiological relationship could not be established between opiate use disorder and suicidal behavior (Nobile et al. 2020). It has been known that there is a relationship between them, but the contradictory data obtained from the studies couldn't provide a clear mechanism. Even so, it was reported that the opioid system was a potential target in the treatment of depression et al. 2009, Peciña et al. 2019). Therefore, new approaches targeting opioidergic dysregulation in depression that suicide is highly frequent may bring novel information in terms of the opioidergic system and suicide relationship.

## Conclusion

The relationship between alcohol/substance use disorder and violent behavior is clear. The violence can be self-directed or towards other people. Furthermore, the comorbidity of alcohol/substance use disorder with mental disorders increases both types of violence. Growing up in a violent environment and being exposed to traumas in childhood are serious factors in the transmission of violent behavior to the next generation. Alcohol/substance use disorders affect not only the users, but also their spouse, children, relatives, neighbors, in short the whole society. Thus, the improvement of violent behavior in alcohol or substance use disorders is necessary for the whole society. A significant part of the studies carried out are originated from developed countries. When we consider the inverse relationship between the development level of countries and violent behavior, the frequency of violent behavior we see in the literature is only the tip of the iceberg. Furthermore, if we consider the cases in which violent behavior has not been reported, the severity of the situation will be better understood. When the relevant literature is examined, the findings obtained from genome studies, animal experiments and neuroimaging studies show that substance use disorders and violent behaviors have a strong biological basis.

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