

Serotonin Deficits as a Factor in Suicidal Behavior a Critical Review

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ABSTRACT

Serotonin neurotransmitter levels and receptor site dysfunction have been indicated as a potential factor influencing suicidal behaviors in individuals with major depressive disorder and in individuals with a history of suicide attempts. The serotonin system's abnormal activity is associated with an increased risk of suicide for those with MDD and a history of suicide attempts, however full understanding of the complex relationship between the serotonin system and suicide is still elusive. Despite this lack of firm understanding, progress is being made towards clinically useful tools and models. This paper analyzes scholarly research articles and provides a critical review of the current state of the field of research.

Suicide is a national epidemic with over 3000 deaths per month attributed to suicide in the United States [1]. The current Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines suicide as a symptom of Major Depressive Disorder (MDD) or Borderline Personality Disorder [2]. However, it also suggests that Suicidal Behavior Disorder may become a validated disorder in future editions. The criteria used to define this potential future inclusion in the DSM-5 provide an important perspective of understanding the biological basis for suicide with criteria that separate it from suicidal ideation or other self-injury diagnosis [2]. The current inclusion of suicide as a symptom of MDD is where much of the current research is being conducted. A full understanding of the relationship between depression and suicide has long been sought but continues to elude researchers despite the significant progress that has been made in recent decades. One specific area of research began with a discovery over four decades ago when the neurotransmitter serotonin was observed in lower than normal levels in the cerebrospinal fluid of suicide victims [3]. This began a long journey to discover and understand the complex nature of the serotonin system and its relationship with suicide.

Background on Suicidal Behavior Research

Suicide is a complex and complicated behavior. Suicide has many contributing factors and has been studied from various perspectives including socially, emotionally, and biologically. Scientists continue to build models of risk factors, behaviors,

biological responses, and protective factors in an attempt to create a whole system view of the issue. Of the components, the biological aspect has been particularly difficult to resolve into finite mechanisms, system dysfunction, and causation.

Much of the research into the biological aspects of suicide has focused on the brain and its ability or inability to regulate stress response and feelings of helplessness. The neurobiology of suicide has many factors including structural brain circuitry and connectivity, genetic and epigenetic factors, neuroinflammation, and serotonin system dysfunction [4]. Neurobiological suicide research has focused on the different sections of the prefrontal cortex including the ventromedial, medial, dorsolateral, ventrolateral, and anterior cingulate cortex [4]. Suicide attempters are observed to have decreased function in some of these areas leading to decreased learning potential in complex environments, language fluency issues, and impaired cognitive control, but research does not all agree on the mechanisms and processes that relate each to suicide [4]. In addition, the effects of genetic and epigenetic factors are thought to be mediated through gene expression of many of the bodies' biological systems which again are not completely understood, including the serotonin system [4].

Serotonin is an important neurotransmitter providing a wide range of functions in the brain and digestive system. It has been considered a biomarker for suicide for the last 40 years,

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ever since it was discovered that the serotonin levels in the cerebrospinal fluid (CSF) of suicide fatalities were significantly lower than those who did not attempt suicide [3]. Since that time further studies have shown that low serotonin, specifically metabolite 5-hydroxyindoleacetic acid (5-HIAA) as measured in cerebrospinal fluid, is indicative of suicide risk in a subpopulation of clinically depressed individuals [4].

Deficits in observed and measured serotonin levels are also not due to a lack of production of the neurotransmitter or its precursor components and enzymes because those were observed at elevated levels in some suicide victims [4]. A likely suspect is the activity of serotonin autoreceptors in a dysfunctional attempt to reduce serotonin activity leading to decreased serotonin neuron firing which in turn is thought to be responsible for the increase in helplessness and quitting behaviors [5].

Does Low Serotonin Contribute to an Increase in Suicidal Behavior

Low serotonin metabolites such as 5-hydroxyindoleacetic acid (5-HIAA) has been observed in multiple suicide victims via postmortem analysis of their cerebrospinal fluid [4]. This low level of serotonin as observed in the cerebrospinal fluid (CSF) does not seem to be based solely on a genetic cause or defect. The deficiency cannot be linked to a genetic predisposition for low production of serotonin, but it has been shown in animal studies that the serotonin uptake system's epigenetic gene expression can be altered due to long-term exposure to anxiety and depression [6].

There has been additional research that reports low serotonin levels alone in healthy individuals are not predictive of suicide nor is it predictive in individuals who suffer only from major depression [7]. The serotonin levels alone are not predictive of a suicide attempt but become more associated as a risk factor for suicide lethality in those individuals who also have a Major Depressive Disorder (MDD) and a history of suicide attempts [4]. Low serotonin levels are associated with suicidal ideations in individuals with MDD. The research is now focused on the genetic expression of the serotonin transport molecules and their regulation in response to and in conjunction with a variety of internal and external factors such as MDD to find the physiological differences in the serotonin system in individuals with past suicide attempts and those without.

Critical Review

Underwood et al., conducted a study to compare serotonin binding activity in the brain cortex between suicide, major depressive disorder (MDD), and alcohol disorder (AUD) fatalities [8]. The authors hypothesize that early childhood adversity affects the serotonin system and increases the risk for enacting suicide, MDD, and AUD [8]. They designed their study to discriminate serotonin receptor binding effects from those of MDD and AUD in postmortem analysis [8].

The study included a large sample size with 232 cases reviewed with all but 65 of those receiving psychological autopsies [8]. The next of kin of a majority of the cases agreed to psychological autopsy interviews and all of the diagnosis or lack of diagnosis was done in concert with experienced psychiatrists and psychologists [8]. Blood toxicology and blood/brain alcohol levels were used

to determine findings of AUD along with examinations of the liver [8]. Victim's brains were bisected after autopsy and only the right hemisphere of the prefrontal cortex was sliced for imaging of serotonin binding using Cynomipramine, 8-OH-DPAT, and Ketanserin for 5-HT_{1A} and 5-HT_{2A} receptor binding sites respectively [8]. Receptor binding was derived from multiple tissue sections and averaged together to produce a single value for each individual [8]. Autoradiograms were taken of each section and measured for serotonin 5-HT_{1A} and 5-HT_{2A} receptor binding sites and serotonin transporters [8]. Using these images, the authors were able to quantify the serotonin activity and compare it to investigative results of AUD, MDD, suicide, and childhood adversity while accounting for age, sex and aggression [8].

Accounting for age, gender, and aggression, the values were compared in several ways to identify the significance or non-significance between MDD, AUD, and suicides [8]. The results were mapped onto 9 areas using Brodmann's regions of the brain. The study found that serotonin messenger levels in suicide deaths were non-region specific using Brodmann's regions, but across the board were higher in individuals with MDD, those nondepressed suicide victims, and the control group, but dropped for individuals dying by suicide who were also comorbid with MDD [8]. While there are more serotonin transporter molecules present in AUD victims, suicide did not have a significant effect and neither did childhood adversity on these levels and there were no region-specific effects [8].

The study compared the results from the serotonin messenger 5-HTT to those of the 5-HT_{1A} binding sites. Again, no significance was found between the activity of the 5-HT_{1A} binding sites and pure suicide in totality or by Brodmann region [8]. MDD also did not show a significant interaction with suicide or the Brodmann region for the 5-HT_{1A} binding sites [8]. The AUD did show an effect with 5-HT_{1A} binding sites having increased activity but only with suicides and not MDD or MDD plus suicide [8]. When childhood adversity was added to the model, non-suicides were associated with higher 5-HT_{1A} binding site activity while the other factors had no interaction [8].

The study's last component looked at 5-HT_{2A} binding site activity and interaction. It was found that pure suicide did not affect binding activity by itself, but when coupled together with MDD it showed an increase over those non-suicidal with MDD [8]. AUD did not have a significant association and neither did any of the Brodmann regions, but childhood adversity did associate with higher levels of activity for 5-HT_{2A} receptors [8].

It is important to note that 5-HT_{1A} and 5-HT_{2A} are both serotonin receptors but have different functions. 5-HT_{1A} is a presynaptic autoreceptor that binds to serotonin and is associated with the activation of a variety of hormones including cortisol, adrenocorticotrophic hormone, oxytocin, and others, but its most important function regarding suicide is as an inhibitor of 5-HT neuron cell firing [9]. These receptors when blocked lead to increases in serotonin levels while the 5-HT_{2A} receptor is an excitatory receptor activating increases in 5-HT activity [9].

When looked at holistically, serotonin messenger activity was lower in suicides but was dependent on an MDD diagnosis [8]. Higher messenger activity was also associated with AUD but

only in suicides, along with higher 5-HT1A receptor binding [8]. 5-HT2A receptor bindings were higher in suicides once the effects of AUD and MDD were taken into account [8]. Lastly, childhood adversity was associated with higher activity and levels of all three: 5-HTT, 5-HT1A, and 5-HT2A [8].

This study displayed several strengths including sample size and multiple variables which all are affected by the serotonin system. The study demonstrated that even though other psychological effects may be occurring as a result of lower or higher serotonin levels, they are only related to suicide in a specific subset. Another strength of the study was the incorporation of psychological autopsy and diagnosis postmortem. This emphasized clinical diagnosis which became important when accounting for comorbid diagnoses in the statistical analysis of the data [8]. This allowed insight that captured relationships between diagnosis and biological changes to the serotonin system.

Methodological limitations

The limitations of this study include those often mentioned in postmortem studies which is that it was cross-sectional and cannot provide insight into causality [8]. Because the study used deceased subjects, the possibility remains that diagnoses could have been missed that were comorbid because of non-reporting or if a psychological autopsy was not performed [8]. The fact that only single-time data points are gathered means that mechanisms and their responses to environmental factors cannot be observed and temporal data cannot be evaluated which may have a bearing on future therapeutics. There are limitations inherent in one-time data capture that prevent identifying changes in genetic mechanisms that may be involved [8].

Another limitation of Underwood's study is the fact that no region-specific information was associated between any of the factors across the large number of case studies. This indicates that either the method of dissecting the cortex or the Brodmann regional atlas may not be sufficiently precise enough to determine relationships. In addition, to the regional divisions used, the resolution of the images may not be detailed enough to determine differences at the proper scale.

Elizabeth Bartlett et al., took the research conducted by Underwood and others and focused a study on the serotonin transporter and receptor sites in current living patients by same-day positron emission tomography (PET) [10]. The study focuses on suicide attempters and a control group consisting of clinically depressed but non-suicidal individuals. To assess the interplay between the factors affecting the observed dysfunction in the serotonin system both groups were selected based on their meeting the criteria for MDD as defined by the DSM-IV by experiencing a recent depressive episode [10]. The study question focused on the neurobiological relationship between major depressive disorder (MDD) and suicidal behavior observed as serotonin brain receptor activity and acute stress in participants with a history of suicide attempts. The study attempted to limit the influence of other factors through the exclusion criteria such as drug use likely to affect serotonin levels, any history or diagnosis of schizophrenia, drug or alcohol abuse in the recent past, head injuries, pregnancy or post-partem, and any history of psychosis or bipolar disorder [10].

The study made use of several clinical tools to attempt to gather as close to real time information about the functioning of the serotonin system as possible. The primary tool used was the positron emission tomography (PET) scan of participants' brains. The PET scans were used to map the serotonin 5-HT transport molecule (5-HTT) and serotonin receptor 1A (5-HT1A) function across the different regions of the brain. These scans were conducted in every case but one, on the same day as the suicidal attempt. The scans consisted of multiple iterative images which were then compared using two separate brain atlases [10]. Copenhagen University Hospital Neurobiology Research Unit (NRU) developed a serotonin binding site atlas of 10 brain regions [10]. This atlas mapped 5-HTT and 5-HT1A, 5-HT1B, 5-HT2A, and 5-HT4 binding sites across 10 geographic regions of the brain that were non-traditional anatomic divisions of the brain and were created specifically for their uniformity and density of serotonin receptors [11].

The serotonin system has one of the most diverse receptor complexes, with 7 families and 14 subtypes of receptors that all use the serotonin transmitter to communicate a variety of messages [12]. The fact that the density of these receptors does not fit neatly into the anatomical division of the brain led to the selection of the NRU atlas in addition to the older Brodmann Area-Based in-house atlas which only separated the regions of the brain into 6 areas. Each of these 6 areas had fewer uniform results as the NRU model and the Brodmann atlas was viewed as secondary to the NRU atlas for this study [10]. These scans and the corresponding plots of active serotonin transporters and binding sites were analyzed and then compared to the results from a second tool.

The second tool used in this study was an ecological momentary assessment (EMA). The EMA was used to collect temporally randomized in vivo stress data from participants to gauge the level of acute stress and helplessness via a cell phone. Few studies attempted to collect real-time data on participant's stress levels and often relied on retrospective reporting and collection of this information [10]. The use of short cell phone prompts throughout the day allowed for the minimization of bias and retrieval issues by the participants. This data was combined with a PET scan from the same day as the suicide attempt to create brain maps of regions of higher or lower 5-HTT and 5-HT1A activity [10]. The scans were compared across the participants for regional or global correlations.

The in vivo study of 1A receptor binding and EMA collected stress levels provided some insight into the nuanced function of the serotonin system of the brain. The brain scans of suicide attempters and non-attempters did not show a significant effect of EMA stress on serotonin binding site function [10]. This result was compared between both the NRU atlas and the Brodmann atlas. When viewed across the study participants, the effect of EMA recorded stress was not significant. When viewed on a brain region-specific basis, there was a significant difference in serotonin activity between attempters and non-attempters in multiple regions [10]. The correlation was stronger for the previous suicide attempters than for the non-attempters. Previous suicide attempters showed lower serotonin transporter 5-HTT in several regions, while non-attempters did not. They also recorded significant binding site differences and a correlation with EMA

stress in most regions for the previous attempter group, which was absent from the non-attempter group [10]. The fact that there was no significant difference in recorded EMA stress between the two groups either during the study or recorded during childhood leaves the only differentiating factor as a previous suicide attempt. Both Brodmann and NRU atlas models agreed on the significance with the NRU model being a stronger case [10].

There are many strengths of this study including capturing real time data on serotonin messenger density and binding site activation by brain region. The inclusion of the newly developed NRU serotonin brain atlas is a strength of this study, and its more detailed region-specific results are a testament to the improvement over the older Brodmann atlas. One of the study's strengths is the specificity in which it used a targeted subset of binding sites for its analysis. Another is the criteria for creating a sample of similar stressed or depressed individuals that could focus on the effects of acute stress on serotonin regulation. The study was able to highlight how past suicide attempts are still the single biggest risk factor and predictor of future suicide and coupled this knowledge together with new insight into how possessing this factor affects the way the body responds to stress via the serotonin system. It added yet another layer of knowledge onto the complex relationship between serotonin and suicide.

The study also discussed the need for future research into how different early-life adversity, genetic allele expression, and current stressors may affect the initial suicide attempt risk. The need for understanding the transformation the behavior and role of the serotonin system undergo during a suicide attempt is not well understood and is an area that needs additional research. Bartlett et al., also discuss the need for more in vivo studies that give more understanding to the mechanistic and physiologic processes that influence feelings of helplessness, suicidal ideation, and suicide attempts that have often been studied only postmortem or filtered through memory recall [10].

Methodological limitations

The in vivo serotonin transporter and 1A receptor binding potential and EMA of stress in major depression and suicidal behavior study that Bartlett et al., conducted was a strong study with a focused premise [10]. However, it was lacking in several ways that could have advanced the science. The study limited itself to the investigation of participants who were screened and qualified as suffering from major depressive disorder. While it was key that the study separated the participants by previous suicide attempts, a more global understanding could have been achieved with the inclusion of a healthy control group undergoing acute stress. This may have revealed additional insight into the changes to serotonin binding and density of messenger molecules that transpire between healthy individuals, those suffering from depression, and those who progress to suicide. The study limited itself to only the 1A receptor sites despite the NRU atlas having many others mapped out. This may have been able to provide more fidelity to the results. The study results did hint at possible permeant changes that may have occurred to the serotonin function or its effects on behaviors in individuals who have experienced a suicide attempt and adjustments in the sample population and size may yield those insights.

This brings up another critique of the study and one the authors acknowledge, which is the small sample size. Statistical analysis such as is relied upon for establishing not only the significance of results but when using large models of unique individual brain chemistry, hinges on having a large sample size. The larger the sample size, the more reliable the data. As it was reported, one of the compromises in the NRU model was to use a wider area sensitivity in the scans for data smoothing [10].

A larger sample size will also account for other temporal or geographic differences that may relate to the study results or variations. There was no indication that time of year or location were explored variables. While age, sex, and psychiatric background were accounted for within the study, additional variables could have been captured such as genetic heredity background, location, employment type, and time of year. The last three relate to possible varying amounts of sunlight each was exposed to and the first relates to any genetic differences that may affect serotonin system dysfunction.

The authors also note that additional longitudinal studies are needed to test whether the serotonin system has any mediating effects on suicidal tendencies in individuals diagnosed with major depressive disorders [10]. Another area for continued improvement is that the study did not have a robust biological basis observed in animal studies. This may partially explain why changes to the serotonin binding and messenger activity were not statistically significant for MDD and acute stress effects absent a history of suicide attempts. A remedy for this would be valid mouse or animal studies of this phenomenon. Many mouse studies of MDD have been conducted in several countries, the fact that they were not included or referenced in this study speaks to the thoroughness of the authors and hints that perhaps a more interdisciplinary team may be required for follow-up studies. This may identify confounding factors or mechanisms that explain the inconsistency.

Another area of critique is that the authors do not mention any reasons why the observed lower levels of serotonin in the cerebrospinal fluid in suicide victims would not be consistent with a drop expected to be observed in suicide attempters. Other parts of the nervous system may contribute to the differences, but this was not explored or addressed.

One of the underlying intentions of the previous two studies analyzed was the goal of furthering the science towards a useable clinical diagnostic tool such as a biomarker. An observation of patients with major depression suffering from increased suicidal ideation is a common complaint about the medications used to treat depression and served as the inspiration for further study of the pharmacogenomics of Consoloni et al., [13]. They designed a study to determine if they could do just that. The authors attempted to show that the gene expressing the serotonin transporter molecule could be used in a predictive way toward suicide attempts and suicide ideology. Building upon the subgroups identified by other research, Consoloni et al., postulated that the expression of the serotonin gene SLC6A4 could be used as a predictor for worsening of suicidal ideation and increased risk of suicidal attempt in a defined timeframe [13]. Previous studies had expressed an association in some but not all results regarding the 5-HTT polymorphism with SLC6A4 mRNA [13].

In order to achieve this goal, the authors built a study with 148 adults who were diagnosed with a recent Major Depressive Episode (MDE) and added to the sample group 100 healthy control subjects [13]. Both groups were screened for drug use, schizophrenia, pregnancy, and severe medical disease. The study took place across 2 time periods and 6 separate cities [13]. Participants were evaluated for depressive symptoms using a short 12-question survey. An important part of the validity of the study design was the reproducibility of the SLC6A4 mRNA expression measures [13]. Using multiple iterations, the procedure and PCR results were validated for the control and MDE groups. mRNA was obtained from leukocytes removed from sample blood taken from the participants [13]. Once the mRNA was filtered and replicated, it was used to amplify the alleles responsible for expressing the 5-HTT molecules which was used to calibrate the baseline from which the variable data would be compared [13]. Once 30 weeks' worth of data had been collected, statistical analysis was performed and reported [13].

The results obtained from the study showed a much lower level of gene expression for SLC6A4 in MDE participants at the beginning of the study when compared to the control group [13]. A full 25% of the MDE participants experienced a depressive episode during the first eight weeks of the study [13]. The data showed that there was no significant difference between the expression of SLC6A4 at the beginning of the study and the eight-week mark for those individuals who did not suffer from a major depressive episode during that period, while the 25% that did show a decrease in SLC6A4 expression [13]. The results of the gene expression were associated with the worsening of suicidal ideation captured weekly by the surveys [13]. The study was broken into two phases with phase one capturing the baseline data and week zero through week eight, and phase two capturing week nine through 30 [13]. During the second phase only 95 MDE patients and 91 control group members participated [13].

One of the most impressive findings from this study was the fact that by week two the SLC6A4 expression was predictive of the increase in suicidal ideation. Statistical analysis showed that both phase one and phase two were consistent in their association of SLC6A4 activity and the status of suicidal ideation or risk. During phase two five participants attempted suicide. When the phase two data was collected and compared to the survey's and recorded clinical data, the expression of SLC6A4 was predictive of the suicide attempt [13]. What was surprising was that this held true for the small collection period of phase one, with week zero through eight data able to predict a suicide attempt before week 30 over 70% of the time [13].

These results clearly stand out as one of the major strengths of this study. Another strength is that both primary and secondary hypotheses were confirmed as the gene expression was positively associated with deteriorating suicidal ideations and with the increased risk of suicide attempts. The study was designed to account for gender, age, BMI, education, location, and time differences [13]. It also captured data including medications, family history, marital situation, and depression quantifying surveys [13]. This gave the study a robust foundation and allowed for the testing of many variables to see if they were associated with any effects on the SLC6A4 gene expression. Another item that this study did well was the negative associations recorded as

part of the data collection. During the intake clinical information was gathered on previous suicide attempts, depression severity, and childhood trauma [13]. All three of these factors had negative findings for any future decreasing suicidal ideation or suicide attempts. Lastly, the authors successfully showed that using serotonin mRNA is stable across longer time frames creating the possibility of its future use as a biomarker for predicting suicidal ideation and attempts.

Methodological limitations

The main limitation of this study is that the investigated potential biomarker is only applicable to major depression disorder patients. It was also a first-of-its-kind study, so there are no similar studies yet to replicate the results. One of the strengths of this study is a primary complaint about many similar ones, the sample being too homogeneous [13]. Many other studies looking for biomarkers had samples that were too homogeneous in order to capture a specific type of population with clinical diagnosis. Another limitation of the study was that the sample size was not that large [13]. When describing potential gene expression factors, patient medication, specifically anti-depressants could have unknown effects on SLC6A4 expression, because the long-term effects of these drugs on this gene have not been studied in detail [13]. Finally, the authors admit that they do not have a firm understanding of the epigenetic factors and mechanisms that affect the variation in mRNA expression from SLC6A4.

There are some common limitations to these studies. All the studies reviewed were unable to address any epigenetic or genetic causes or mechanisms associated with serotonin dysfunction in suicide attempts, suicide cases, or suicide risk. The understanding of whether the observed serotonin system differences are translational, transcriptional, or post-translational genetic changes continues to be a need for future research. Another limitation is the lack of understanding of the role serotonin plays in the lethality of suicide attempts. While depressed levels of HTT have been observed in suicide deaths, those same levels of drops are not always observed in suicide attempts and it is ill understood what role these lower levels play in the lethality of the attempt.

Another limitation is the lack of a sufficient model of how environmental stimulus leads to serotonin inhibition with a resulting suicidal impulse. Popova et al., talk about the kynurenine pathway and its degradation of serotonin and melatonin levels coupled with a rise in inflammation messengers, specifically QUIN quinolinic acid, which is observed in increased levels in the spinal fluid of suicide attempters regardless of the presence of comorbid disorders [14]. This speaks to a general oversimplification of the role of serotonin in the research questions in the studies reviewed. While serotonin is clearly observed in decreased levels in CSF and often in the prefrontal cortex and other parts of the brain, it has not been proven to show causation. More likely as was mentioned in many conclusions, it is just one part of a more complex interrelated process.

One of the most glaring absences in suicide prevention and risk mitigation is the lack of clinical tools such as biomarkers that can provide diagnostic evidence of suicidal risk. As was discussed earlier, the current state of knowledge has determined relationships under certain conditions exist between a major depression diagnosis, suicide risk, and the serotonin system,

but no definitive bio-markers have been validated. There are several reasons for this as Johnson et al., point out, many neuropsychiatric disorders overlap symptoms with each other which complicates the predictive validity of using suicidal ideation towards quantifying suicide risk [15]. Determining suicidal risk has traditionally been a subjective endeavor with many clinical interpretations and cultural influences affecting reporting and diagnosis. Also complicating data collection and model development is the established issue of suicidal attempts, suicidal ideations, and death by suicide may not have the same mechanisms and therefore have different biomarkers [15]. The frustrating part of this conundrum is that clinicians have often treated them as one and the same. Without a way to clinically differentiate them, designing studies to find separate biomarkers for each is an additional challenge.

Another issue that Johnson et al., point out is although genetic and epigenetic biomarkers can be measured in several ways, they are difficult to determine in postmortem cross-sectional studies, and the predictive quality is degraded because of a lack of individual baseline comparisons [15]. What is needed is longitudinal studies to help identify the mechanisms and the specific changes they undergo in response to various stimuli that increase the suicide risk, but with research showing ideation, attempts, and actual suicide becoming more distinctive, the challenge remains significant.

Future Research Directions

Studies have shown that lower levels of serotonin have been observed in the brains of suicide attempters, but others have shown that some suicide attempters do not exhibit the same drop in serotonin levels or that those drops are not associated with suicidal behaviors [16]. Popova et al., suggest that lower levels of serotonin may not be directly responsible for depression and suicidal ideation, but a victim of serotonin precursor enzyme metabolism by the kynurenine pathway into the inflammation response [14]. This is one possible explanation and presents a future area of research.

Other areas of needed research include expanding upon the understanding of the genetic mechanisms responsible for changes in serotonin levels in a wider population of suicidal individuals. With the breakthrough in finding a gene that has altered the expression of serotonin molecules in response to epigenetic conditions involving Major Depression Disorder, the door is open to finding other conditions and genes that are associated with suicidal tendencies. Understanding the factors that influence the exact changes will be part of the complex picture of serotonin's role in suicide. Another area prime for future research is to not only understand the physiologic differences in individuals who have experienced a suicide attempt, those who committed suicide, and those with only suicidal ideations but to confirm and validate proposed and postulated biomarkers for robust clinical application for each [15-23].

In conclusion, serotonin's role in suicide, whether it is suicidal ideation, suicidal attempts, or commitment of suicide is a complex interaction of multiple physiologic, genetic, and environmental factors. Research to date has been successful in identifying the subtle differences between ideation, action, and lethality when it comes to suicide and serotonin, but much work remains to be done. As new potential candidates for bio-markers

are presented for future validation, the field will need continued focus and perseverance to make these breakthroughs useful to the patients and clinicians who need them.

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