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Adolescent Angst or True Intent? Suicidal Behavior, Risk, and Neurobiological Mechanisms in Depressed Children and Teenagers taking Antidepressants

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ABSTRACT: *Suicide is one of the major causes of morbidity and mortality amongst children and adolescents. In 2004 the Food and Drug Administration (FDA) issued a "black-box" warning for antidepressants in children and adolescents, stating that these drugs may increase suicidality, a term encompassing both suicidal thoughts and behavior, especially in the first few weeks of treatment. The warning was extended in 2007 to antidepressants prescribed to adults aged 25 and under. The evidence behind this decision stemmed from meta-analyses of antidepressant clinical trials that demonstrated a slight increase in suicidality in those receiving antidepressants versus those treated with a placebo. Due to methods of this pooled data compilation, the relationship between antidepressants and suicidality remains controversial. This report investigates a case where a 14 year old with major depressive disorder (MDD) developed suicidal ideation shortly after being prescribed a selective serotonin reuptake inhibitor (SSRI). Investigating the role antidepressants may play in suicidality suggests the need to explore the neurobiological mechanisms within the serotonin system. This case and its theoretical explanations attempt to bridge the gap between neurobiology and pharmacology in order to better delineate the etiology of this adverse effect.*

KEY WORDS: *Antidepressants, MDD, Pediatrics, serotonin, SSRI, suicidality.*

ABBREVIATIONS: *Selective Serotonin Reuptake Inhibitor (SSRI), Major Depressive Disorder (MDD), Pediatric Bipolar Disorder(PBD).*

INTRODUCTION

Major depressive disorder (MDD), a mood disorder common to both adults and children, can cause suicidal ideation and actions. Antidepressants are the major pharmacologic intervention for treating MDD (Brent & Birmaher, 2002) and can ideally decrease a person's risk of suicidality. Low levels of serotonin or serotonergic activity are a known precipitant of depression and Selective Serotonin Reuptake Inhibitors (SSRI), a class of antidepressants, work to increase the amount of serotonin in the brain (Blier, 2001; Brent, 2004; Mann, Brent & Arango, 2001). Paradoxically, SSRIs, the very treatment intended to decrease an individual's risk of suicide, may trigger these thoughts as well (Brent, 2004; Brent, 2005). What is the role of SSRIs in precipitating suicidal ideation? This paper investigates theoretical mechanisms that could account for this side effect within the brain by exploring the neurobiological framework for increased suicidal ideation in patients who are initiated on SSRIs. Various serotonin receptors, such as the 5-HT1a receptor, are modulated in the beginning stages of treatment with the SSRI (Blier, 2001; Celada, Puig, Amargos-Bosch, Adell, & Aragas, 2004). The 5-HT1a receptor is found both pre-synaptically and post-synaptically (Barnes, & Sharp, 1999; Blier, 2001; Celada, Puig, Amargos-Bosch, Adell, & Aragas, 2004). In their pre-synaptic form, 5-HT1a receptors function as a negative feedback mechanism (Blier, 2001; Celada, Puig, Amargos-Bosch, Adell, & Aragas, 2004). Initially, with an SSRI, there is more negative feedback via these receptors to the pre-synaptic neurons, effectively dampening the firing rate of serotonergic neuronal projections to other parts of the brain. It has been postulated that this leads to a net decrease in the overall serotonin activity (Celada, Puig, Amargos-Bosch, Adell, & Aragas, 2004; Gartside, Umbers, & Sharp, 1997). As time goes on, these receptors are desensitized, leading to an increase in serotonin at post-synaptic receptors (Blier, 2001; Celada, Puig, Amargos-Bosch, Adell, & Aragas, 2004). This mechanism may explain why, when there is a lull in serotonin activity in the initial stages of SSRI treatment, some children and adolescents experience increased or new-onset suicidality.

The controversy over antidepressant prescriptions in children and adolescents began over a decade ago. In 2003, the Medicines and Healthcare products Regulatory Agency (MHRA), the British equivalent of the Food and Drug Administration (FDA), began an investigation into antidepressant prescriptions in children based on evidence from internal corporate studies demonstrating increased rates of suicidality in paroxetine trials (Ho, 2012; Savitz, Lucki, & Drevets, 2009). After reviewing clinical trial data from SSRIs and Serotonin Norepinephrine Reuptake Inhibitors (SNRI), the MHRA advised that prescriptions of antidepressants, with the exception of fluoxetine, be banned in those 18 and younger (Goode, 2003; Levin, 2009). The MHRA argued that the risk of suicidality outweighed their potential benefits. The agency also concluded that antidepressants had limited efficacy in treating MDD in the children and adolescents (Levin, 2009).

Shortly after the MHRA queries, the FDA launched its own investigation. Using experts in adolescent suicide and mood disorders, they re-classified 24 prior randomized controlled trials to explore the risk of suicidality in those prescribed antidepressants versus those taking a placebo (Levin, 2009). The meta-analysis showed a 1.8 fold increase in the rates of suicidality symptoms when the results of multiple randomized, controlled trials were pooled (Brent, 2005). The results showed an increase in suicidality of about 4% in those with an SSRI versus only 2% in those prescribed a placebo (Dopheide, 2006). While these results are unequivocal, the re-classification scheme remains controversial because the clinical trials reviewed coded adverse events, such as suicidality differently

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and did not measure suicidality as an endpoint (Ho, 2012). Many in the medical profession remained skeptical of the FDA's findings.

The results from the FDA's warnings have had numerous effects. The series of warnings and the publicity on the topic had a profound effect on the public's opinion of antidepressants and the prescribing practices of physicians (Cheung, Sacks, Dewa, Pong, & Levitt, 2008). For example rates of antidepressant prescriptions declined amongst primary care providers by 58% and the number of children diagnosed with depression also fell substantially (Libby, Brent, Morrato, Orton, Allen, & Valuck, 2007). These 'black box' warnings also potentially influenced the suicide rate of children and adolescents. For example, data from the Centers for Disease Control and Prevention (CDC) estimated that suicide rates increased 8% in 2003 to 2004, which was the year of the initial warnings and the height of the controversy (Centers for Disease Control and Prevention, 2007; Cheung, Sacks, Dewa, Pong, & Levitt, 2008; Libby, Brent, Morrato, Orton, Allen, & Valuck, 2007). However, it cannot be determined if this was related to the regulatory warnings themselves.

This is a relevant and important topic as suicide is a major cause of morbidity and mortality in children: it is the third leading cause of death amongst adolescents' ages 10-24 ages (Centers for Disease Control and Prevention, 2014). The morbidity from self-harm behavior is also at epidemic levels, with approximately 157,000 annual emergency room visits from adolescents aged 10-24 due to self-injurious behavior (Centers for Disease Control and Prevention, 2014). Yet, ten years after the initial investigation into these adverse effects, the regulatory warnings remain but the relationship between antidepressant use and suicidality remains equivocal, requiring further examination at the neurobiological level. As the following case illustrates, there is some weight to the FDA's warning as children can experience suicidality from SSRIs.

CASE

A 14-year-old girl with a history of ADHD, inattentive type and no prior history of psychiatric medications, presented to her psychiatrist with anxiety. A few months prior, the patient had tried cannabis, which induced panic attacks during intoxication. Since this event, and despite sobriety, she had recurrent panic attacks, rendering her agoraphobic to avoid triggers. She developed depression secondary to these events. During intake, she met DSM-IV criteria for MDD, admitting to depressed mood, guilt, poor concentration, sleep and appetite. In addition, she also met criteria for premorbid generalized anxiety disorder and had lost 10 pounds due to her anxiety and depression. She denied mania, psychotic symptoms, eating disorders, substance abuse (outside of initial cannabis use), suicidal or homicidal ideation. During the mental status exam she appeared her stated age, was cooperative with normal speech. She had no abnormal movements or tics. She described her mood as "anxious" and her affect was dysphoric and constricted. Her thought process was organized and her thought content did not reveal any suicidal or homicidal thoughts, delusions or obsessions. Her attention was good, her concentration fair and she had good insight and judgment. She had seen a mental health specialist in the past, had never been on psychotropic medicines, been hospitalized or attempted suicide or had suicidal thoughts. She had no other past medical history, no allergies and denied caffeine use. She performed adequately in school. She had a family history of depression, anxiety disorder, ADHD, and substance abuse.

The patient was started on sertraline 25 mg. She and her mother were educated on the worsening symptoms of depression and about SSRI side effects, including suicidal ideation. The patient was offered and declined cognitive behavioral therapy (CBT). Six weeks later, the patient presented to her therapist with increasing passive suicidal and homicidal ideation without any apparent stressor. Sertraline was discontinued. The following day, she sought further evaluation at the emergency department (ED) after failure of her support and safety plan. In regards to safety, the patient and her mother had been educated prior to the lethality risks associated with antidepressants and how to monitor for those symptoms. They were instructed to contact the prescriber if needed. Despite acting on these instructions, counseling via phone to stop the antidepressant and increased monitoring by family members, her new onset lethality symptoms were risky enough to warrant an emergency evaluation. The patient was experiencing increased suicidal ideation as well as homicidal ideation and both had changed from passive to active in nature. She felt she was a danger to herself and possibly others. After admission to the ED for observation, she was discharged the next day and went back to outpatient treatment, where she reported no current suicidal or homicidal ideation after 48 hours off sertraline. She was referred for CBT.

DISCUSSION

This case demonstrates the role of SSRIs can have in precipitating and worsening suicidal thoughts even in those without any prior history. However, the risk factors for suicide are complex and varied. Numerous psychosocial and genetic factors increase a person's risk including - substance abuse, mood disorders, head injuries, "impulsive aggressive behavior," and a positive family history (Brent, & Birmaher, 2002; Brent, & Mann, 2006; Mann, 2003). Adoption studies demonstrate evidence for a genetic component in suicide, showing increased rates of suicide amongst the biological relatives of adoptees that have committed suicide (Mann, Brent, & Arango, 2001).

Changes in the serotonergic system are also implicated in suicidality as well as in MDD (Arango, et al., 2001; Mann, Brent, & Arango, 2001; Mann, 2003). Post-mortem analyses of suicide victims show changes in serotonin receptors; there are lower levels of 5-Hydroxyindoleacetic Acid (5-HIAA) a metabolite of serotonin, in the cerebral spinal fluid (CSF) of people who have committed suicide versus post-mortem controls (Arango, et al., 2001; Mann, Brent, & Arango, 2001). Furthermore, low serotonin is itself related to aggressive behavior and impulsivity, which are suicide risk factors themselves (Mann, Brent, & Arango, 2001).

Antidepressants that block serotonin transporters seem to trigger a mechanism that can increase suicidality, at least in the early stages of pharmacotherapy. While the biochemical effects of SSRIs have a rapid onset, their clinical efficacy, defined as a decrease in the symptoms of depression, take weeks to develop (Blier, 2001). It is in this "gap" where the clinical effects lag behind the biochemical effect, that there is evidence for increased suicidality. Therefore, it is necessary to explore the modulation of the serotonergic system in these critical first few weeks of treatment. Most of the increased suicidal thoughts and behaviors demonstrated in the FDA's analysis happened early in clinical treatment.

In the central nervous system, the serotonergic system is a vast network of neurons that project from the raphe nucleus to numerous areas in the limbic system and cortex (Arango, et al., 2001). SSRIs act to increase the amount of serotonin at post-synaptic junctions by inhibiting the reuptake of serotonin into pre-synaptic neurons and leaving serotonin at the junction for a longer period of time. While there are multiple different serotonergic receptors (1-7 with subgroups ranging from a-c), a key receptor implicated in the role of SSRI pharmacology is the 5-HT1a receptor (Barnes, & Sharp, 1999; Gartside, Umbers, & Sharp, 1997; Savitz, Lucki, & Drevets,

2009). The 5-HT1a receptor is located on somatodendritic neurons in the raphe nucleus and post-synaptic neurons, which receive feedback from the raphe nucleus (Gartside, Umbers, & Sharp, 1997; Savitz, Lucki, & Drevets, 2009). The somatodendritic receptors provide negative feedback to the serotonergic neurons in the dorsal raphe and therefore can downregulate responses to the projections of the serotonergic system in the central nervous system (CNS). For example, when a person takes an SSRI, the excess serotonin provides post-synaptic receptors with more feedback and stimulates the 5-HT1a somatodendritic receptor (Celada, Puig, Amargos-Bosch, Adell, & Aragas, 2004). Initially, this net effect appears to cause a reduction in the acute firing of serotonin neurons. Clinically, this acute reduction could explain why some people are at risk for suicidal ideation as the instant negative feedback cuts the net level of serotonin activity. Within a few weeks of stimulation from the SSRI, the somatodendritic receptors desensitize and the negative feedback is downregulated, with now even more serotonin available at the post-synaptic receptors (Gartside, Umbers, & Sharp, 1997; Savitz, Lucki, & Drevets, 2009). This secondary effect likely treats MDD symptoms. As low serotonin levels are known to be present in suicidal patients, this initial robust 5-HT1a dampening of serotonin neuronal activity may add to a low serotonin state, making a patient's depressive state temporarily worse and causing suicidal thoughts and behaviors emerge acutely.

CONCLUSION

MDD is a common phenomenon in both adolescents and children. Suicidal ideation and suicide are important causes, respectively, of morbidity and mortality within this population. While the etiology of suicidality is complex, it is vitally important to recognize suicidal symptoms in patients when they do occur. Though antidepressants are an important and needed therapy to treat depressive symptoms, clinical trials and meta-analyses have shown a link between SSRI usage and suicidality.

This patient with MDD developed both suicidal and homicidal ideation during the first few weeks of SSRI treatment. The nature of her symptoms during the initiation of antidepressant therapy suggests a temporal relationship between the two. Synaptic changes during early SSRI treatment, such as negative feedback from 5-HT1a somatodendritic receptors, and the resultant low net levels of serotonin caused by this mechanism represent one possible explanation for her symptoms. There are limits, however, to exploring the relationship between neurobiological mechanisms and suicidality caused by SSRIs. Why do some people, like the patient in this case report, develop suicidal or homicidal ideation on SSRIs, while others do not? This suggests the need to look for additional underlying mechanisms or to explore other etiologies.

Suicidal and homicidal ideation can be symptoms of diverse psychopathologies. In children and adolescents they can be caused by mania in addition to MDD. MDD itself can also be a harbinger of underlying pediatric bipolar disorder (PBD) (Brent, & Birmaher, 2002; Brent, 2004). Children with PBD may exhibit a more chronic and episodic course than adults, presenting with mixed states and rapid cycling. Suicidal behavior can thus be seen, at least in a subset of these children, as a manifestation of underlying PBD (Joseph, Youngstrom, & Soares, 2009). Additionally, SSRIs themselves are known to trigger mania in adults and children (Brent, 2004). The homicidal ideation reported by this patient could represent the activation of mania or be seen as a type of hostility, another known adverse effect of SSRIs (Brent, 2004; Cheung, Dewa, & Levitt, 2005). While further exploration is beyond the scope of this paper, the fact that children who exhibit MDD when it may be emerging PBD is another confounding variable for clinicians to consider when treating this population.

This case adds further weight to the FDA's controversial "black box" warnings in 2004 and 2007. Clinicians need to be constantly vigilant about the side effects of SSRIs, especially suicidality, even if they are skeptical about the ways the FDA's data was collected or the patient's true psychopathology remains unclear. Educating patients about these serious side effects is critical to helping them monitor their own symptoms. This patient and her family received extensive education about adverse events including mood worsening and lethality escalation. She appropriately followed through with this psychoeducational training and notified her therapist and family when she developed worsening symptoms.

Certain populations may be more at risk than others for developing suicidality during early SSRI treatment. Further bench top and clinical research, regarding pharmacogenetics, slower titration, better patient and parent education are warranted.

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