

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

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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-HT_{1a} receptor, are modulated in the beginning stages of treatment with the SSRI (Blier, 2001; Celada, Puig, Amargos-Bosch, Adell, & Aragas, 2004). The 5-HT_{1a} 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-HT_{1a} 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, which projects 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 (Ho, 2012; Savitz, Lucki, & Drevets, 2009). The MHRA argued that the risk of suicidality outweighed their benefits (Ho, 2012; Savitz, Lucki, & Drevets, 2009).

Using experts in adolescent suicide and mood disorders, the MHRA conducted a meta-analysis to explore the risk of suicidality in those prescribed antidepressants versus those taking a placebo (Levin, 2009). The meta-analysis 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 MHRA reviewed coded adverse events, such as suicidality differently

and did not measure suicidality as an endpoint (Ho, 2012). Many in

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. For example rates of antidepressant prescriptions declined amongst with depression also fell substantially (Libby, Brent, Morrato, Orton, Allen, & Valuck, 2007). These 'black box' warnings also potentially data from the Centers for Disease Control and Prevention (CDC) was the year of the initial warnings and the height of the controversy (Centers for Disease Control and Prevention, 2007; Cheung, Sacks, Fgyc."Rqpi." ("Ngxkw."422:="Nkdd{."Dtgpv."Oqttcvq."Qtvqp."Cmngp." (" 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

A 14-year-old girl with a history of ADHD, inattentive type

cannabis, which induced panic attacks during intoxication. Since this event, and despite sobriety, she had recurrent panic attacks, rendering

2009). The 5-HT_{1a} 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-HT_{1a} somatodendritic receptor (Celada, Puig, Amargos-Bosch, Adell, & Aragas, 2004). Initially, this net effect appears to be acute reduction could explain why some people are at risk for suicidal ideation as the instant negative feedback cuts the net level

