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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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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 ýring 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 þuoxetine, be banned in those 18 and younger (Goode, 2003; Levin, 2009). The MHRA argued that the risk of suicidality outweighed their potential beneýts. The agency also concluded that ae o a ‘

investigation. Using experts in adolescent suicide and mood disorders, they re-classiýed 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-classiýcation scheme remains controversial because the clinical trials reviewed coded adverse events, such as suicidality differently

and did not measure suicidality as an endpoint (Ho, 2012). Many in the medical profession remained skeptical of the FDAôs ýndings.

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

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 ýring 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