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The Effects of Maternal Antidepressant Usage on a Child's Psychological Health

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ABSTRACT

Because of a lack of consistent research, antidepressant usage during pregnancy is a confusing subject for consumers. Results from some studies imply that antidepressant usage during pregnancy for the treatment of depression and other mood disorders can have negative effects on a child. Conflicting evidence indicates that the negative effects potentially caused by antidepressants are not as intense as the effects of untreated depression during pregnancy. Current research on antidepressant usage during pregnancy only examines general health measures in infants and toddlers and does not examine effects on older children who are able to be assessed for potential cognitive and mood influences of perinatal antidepressants. This study investigated the effects of maternal antidepressant usage on psychological development in children at 9-10 years of age and 11-12 years of age. The data showed that perinatal medication usage did not affect children's mental health in early adolescence. The use of antidepressants during pregnancy is potentially safe for the fetus, the childbearing parent, and the child during early adolescence.

Introduction

In the United States, depression is second only to heart disease as a leading cause of medical disability (Michaud 2001). Women are vulnerable to mood instability at times of life-cycle related hormonal changes including pregnancy, post-miscarriage, postpartum and perimenopause (Burt, et al., 2008). There are neurobiological, genetic, and psychosocial factors that influence the increased vulnerability for depression in women (Burt and Quezada, 2009). The impact of maternal depression on maternal and child health, psychological well-being, and other possible consequences of chronic depression are important aspects of mood to examine because of the prevalence of depression in the U.S.

Childbirth is a difficult process that can result in mental and physical health issues. During pregnancy, typical hormone levels are askew leading to mood instability (O'Hara, et al., 1990). Childbearing people are prescribed medications to maintain and balance the hormonal levels. These hormonal changes are often more severe in people with preexisting mental health disorders. For example, childbearing people with clinically diagnosed bipolar disorder who had a severe postpartum episode have a risk of greater than 60% for a severe recurrence following a further pregnancy compared to a risk of around 25% for bipolar people who have not experienced a postpartum episode (Robertson et al. 2005). Studies have shown that during late pregnancy childbearing people experience significantly higher levels of depressive symptomatology and poor social adjustment than non-childbearing people (O'Hara, et al., 1990). It is important to examine more closely the effects of starting or stopping prescription

medications while pregnant because of the vulnerability to depression and other mood disorders that childbearing people have and the associated risks to the child if the parent's mental health is left untreated. Two interesting but detrimental mood disorders that are often a result of these hormonal fluctuations are postpartum depression and perinatal depression.

Postpartum depression is depression in the child-carrying person after they have given birth. Studies have shown that postpartum depression is best treated with antidepressants like selective serotonin reuptake inhibitors (SSRIs) such as Venlafaxine (Cohen, et al., 2001). Although there have been many studies on the effects of maternal postpartum depression on the child and how to treat postpartum depression, there has been significantly less investigation of perinatal depression.

Perinatal depression is when a major depressive disorder occurs before pregnancy, during pregnancy, and up to a year after the child is born. Perinatal depression effects 10–15% of childbearing people (Lee, et al., 2016). One of the biggest concerns with perinatal depression is how to treat it and how the depression and the treatment will affect the fetus and infant. Perinatal mood disorders can manifest in the form of depression, anxiety, obsessive compulsive disorder, post-traumatic stress disorder, bipolar disorder, and psychosis (Jones, et al., 2010). One in seven childbearing people suffers from perinatal mood disorders or anxiety symptoms making it more common than gestational diabetes and gestational hypertension (Wood, 2020). Not only do these mood disorders affect the pregnant person and fetus, but perinatal mood disorders also affect the

infant's health. Research has shown that perinatal mood disorders can lead to low birth weight, preterm delivery, cognitive delays, and behavioral problems in the child (Wood 2020).

To treat perinatal mood disorders, some patients will take antidepressants. There has been discussion on the effects of maternal antidepressant use on cognition and learning in children, and studies have found that there are no effects of antidepressants on the child's cognition (Nulman, et al., 2002). However, the previous study only examined toddlers and did not assess older children or other aspects of mental health. Although research has looked at the effects of perinatal depression and perinatal usage of antidepressants on physical and cognitive processes in infants, there is little research on the effects of perinatal antidepressants on the psychological health of older children which is the focus of this thesis (Deave, et al., 2008).

Previous research has shown that antidepressants taken during pregnancy interact with the fetuses' environment in the womb (Bellissima, et al., 2020). Specifically, studies have shown that in patients that used antidepressants, there was an increase in S100B protein levels in maternal-fetal biological fluids (Bellissima, et al., 2020). S100B protein is involved in multiple cellular processes, like cell differentiation, neurogenesis, neuronal plasticity, and can enhance memory and overall cognition (Bellissima, et al., 2020). S100B can be a glia marker protein because it may be released by astrocytes and oligodendrocytes. S100B protein is an important protein in the brain and has even been used as an early assessment to see if a patient has a traumatic brain injury (TBI). If there are

higher levels of S100B protein that means there is a high level of cell death and in turn a marker of a TBI (Thelin, Nelson, and Bellander, 2017).

The S100B protein was also shown to be an indicator of mood disorders. S100B levels were increased in those with depression and were decreased using antidepressant treatment (Schroeter, et al., 2013). Increased and disrupted S100B protein levels have also been correlated with physical health issues in the fetus and the parent like congenital heart disease and pre-eclampsia (Tskitishvili, et al., 2006; Bokesch, et al., 2002).

There has been previous research investigating the effects of antidepressant usage during pregnancy on the development of the offspring's brain. Specifically, one study found that in a rat model, fluoxetine treatment during rat pregnancy decreased the anogenital distance (the distance from the midpoint of the anus to the genitalia) in juvenile male offspring and in adult male offspring it was found that there was a decrease in the number of intromissions (insertion of penis into vagina), a longer latency to the first intromission, and a longer latency to the first ejaculation (Rayen, et al., 2013). This same study also found that exposure to fluoxetine and/or prenatal stress in the womb decreased the sexually dimorphic nucleus of the preoptic area (SDN-POA) (Rayen, et al., 2013). In addition, it was found that prenatal stress, but not exposure to developmental fluoxetine, decreased the number of tyrosine hydroxylase (TH)-positive cells in anteroventral periventricular nucleus (AVPv) and the volume of the posterior bed nucleus of the stria terminalis (pBST) in male offspring (Rayen, et al., 2013). This data shows that there is some kind if molecular level that antidepressant

usage is affecting. Further research needs to look at what these changes can lead to.

In comparison, other studies have shown that there is no correlation between the use of antidepressants for perinatal depression and increased pregnancy risks (Nordeng, et al., 2012). The current data do not suggest an increased risk of malformations, preterm birth, or low birth weight following prenatal exposure to antidepressants (Nordeng, et al., 2012). Previous research has also shown that neither tricyclic antidepressants nor fluoxetine adversely affected the child's global IQ, language development, or behavior (Nulman, et al., 2002). However, there was a significant and negative association between IQ and the duration of the maternal depression (Nulman, et al., 2002). These data show that there may be a correlation between the intensity and length of the depression and the severity of the defects (mental and physical) on the offspring.

Prenatal depression is extremely important to treat because developmental delays have been seen in children whose birth parent was depressed during pregnancy (Deave, et al., 2008). However, the previous study did not include the use of antidepressants during pregnancy to treat maternal depression. The previous literature has examined the effects of antidepressant treatment for maternal depression on a child's cognition, learning ability (Deave, et al., 2008), and IQ (Nulman, et al., 2002). There is a gap in the literature when it comes to the investigation of the effects of the use of antidepressants during pregnancy on mood related disorders like depression in an offspring later in childhood.

The aim of this study was to investigate the influence of perinatal antidepressant use on psychological development in children aged 9-14 years. Specifically, the child's mood with regards to mood disorders like depression, anxiety, obsessive compulsive disorder, post-traumatic stress disorder, bipolar disorder, and psychosis was examined. We hypothesize that the offspring of childbearing people who took antidepressants during pregnancy will report more negative mental health issues during adolescence compared to the offspring of childbearing people who did not take antidepressants during pregnancy. Using data from the national Adolescent Brain Cognitive Development (ABCD) Study (abcdstudy.org), this thesis examined relationships between mood disorders in children whose birth mother used perinatal antidepressants compared to the children of a birth mother who was not treated with antidepressants during pregnancy.

Methods

Previous data obtained by the Adolescent Brain Cognitive Development (ABCD; abcdstudy.org) study were analyzed to test hypotheses about the relationships between maternal antidepressant use and child mental health measures. The ABCD study is a long-term study of brain development and child health that is currently in progress at 21 sites throughout the U.S including the University of Vermont. Children were included at the start of this study if they met the following criteria: age 9.00 to 10.99 years at time of baseline assessments; able to validly complete baseline assessments including MRI scanning; and fluent in English.

Children were excluded from the study for the following; MRI contraindications such as orthodontic braces or irremovable dental appliances containing ferromagnetic materials, claustrophobia that cannot be overcome with repeated attempts, non-removable ferromagnetic metal implants that may distort the images, or youth is pregnant on day of scanning based on urine pregnancy test in postmenarcheal females; not fluent in English; non-correctable vision, hearing or sensorimotor impairments that may confound the child's responses on the assessments; a history of persistent major neurological disorders such as cerebral palsy, brain tumor, stroke, brain aneurysm, brain hemorrhage, or subdural hematoma (other exclusionary medical or neurological conditions included multiple sclerosis, sickle cell disease, and the following seizure disorder diagnoses: Lennox-Gastaut syndrome, Dravet syndrome, and Landau Kleffner syndrome); gestational age less than 28 weeks and birthweight less than 1,200 grams (2 lb 10 oz). Birth complications that resulted in hospitalization for more than a month are exclusionary (but not if the hospitalization was due to prematurity alone); a current diagnosis of schizophrenia, autism spectrum disorder (moderate or severe), mental retardation/intellectual disability, or alcohol/substance use disorder. (A past diagnosis that has remitted is not exclusionary); a history of traumatic brain injury (TBI): TBI with loss of consciousness >30 minutes, or Amnesia >24 hours, or positive neuroimaging findings (e.g., symptomatic hemorrhage) secondary to TBI; parent/guardian's report that the child would be unable to complete the baseline assessments (i.e.,

answer questions, solve puzzles on an iPad, follow directions, and lie still in the MRI scanner).

Parents were included if they were the primary custodial parent or legal guardian with the child in the home for most of the year. Parents were excluded if they were unwilling to attend annual visits and complete the parental assessments.

If a child and parent pair met all the criteria the children's symptoms and diagnoses and the biological parents' prescription drug and street drug usage was examined. There were 11,880 children who enrolled in the study as 9- or 10-year-olds. They are currently being followed for 10 years and are in approximately year four of the study. Using the Kiddie Schedule for Affective Disorder and Schizophrenia (KSADS; Kaufman et al. 2013)) the children's diagnosis and symptoms data were collected. The KSADS is a semi-structured interview used to measure current and past symptoms of mood, anxiety, psychotic, and disruptive behavior disorders in children ages 6-18 years old (Kaufman et al. 2013). A few examples of questions asked were;

1. In the past two weeks, how often have you felt sad, down, or depressed, with the down feeling lasting most of the day? (Townsend et al., 2020).

The KSADS was updated to assess DSM-5 diagnoses, and it is this version that has been translated into a computerized assessment which the ABCD study uses (Kaufman et al. 2013). The data examined for this research question

were the baseline or first symptom and diagnosis section of the KSADS and the 2 year follow up diagnosis and symptom section of the KSADS for the children.

The biological birth parent was asked whether they took a medication before being pregnant with their child and if they answered "yes" they were asked to list the prescription drugs they were taking. They were asked a similar question again but this time they were asked whether they took prescription drugs while they were pregnant. If they answered "yes" they were then asked to list the names of those drugs. There was space for up to five different prescription drugs to be listed. The subjects were also asked whether they had used alcohol, marijuana, tobacco, heroin/morphine, or crack/cocaine while pregnant with their child. Participants that left any of these questions blank (including the name of the medication) were excluded from the analysis.

To begin, the data for the participants' prescription drug usage had to be sorted and categorized by the class of medication the subject was using before and during pregnancy. The medications were broken up into five different groups: 1 - antidepressants, 2 - opiates, 3 - stimulants, 4 - hormones, and 5 - other (including bipolar medications and over the counter medications). The frequency of specific prescription drug usage was obtained.

In addition to the parents' data, the children's data had to be organized into the KSADS baseline symptom and diagnosis report and the 2-year follow up report. The KSADS consisted of the child being interviewed every year in person and completing a telephone interview at the 6-month intervals between the visits. During these check-ins and visits, the children would answer multiple

questionnaires about many domains of functioning and development including mood and cognition. These data are then compiled into the symptoms and diagnosis report which highlights different mood and cognition disorders like, depression, bipolar, psychosis, schizophrenia, and suicidal ideation. The diagnosis section was separated from the data and analyzed further.

Using the unique NDARs (numbers) that corresponded with each parent and child pair, the children were matched up to the parents. Many of the parents who left the 'yes' or 'no' answers blank or did not identify what type of prescription drug was taken during pregnancy, were not included in the analysis because it could not be confirmed whether there was the presence of a prescription drug while in utero. Only biological parents were included in the analysis. The children were sorted into different groups depending on what prescription and over-the-counter drugs and street drugs the childbearing parent took during pregnancy. There was also a group of children (n=8388) whose biological mother did not take any prescription or street drugs while pregnant with them. About 300 children were randomly selected from this group to be compared with the other groups of children.

Using SPSS, independent samples T-tests were run between the children in the perinatal antidepressant group and the children in the no perinatal prescription or street drug group (control group). Independent samples T-tests between the control group and each prescription drug class and all the street drugs were analyzed as well. This same process was used for the 2-year follow up data. The comparison data between medication and street drug usage to the children's

diagnosis report from the baseline and 2-year follow up were also analyzed to examine any change over time using a one-way ANOVA.

Results

The total number of participants who took prescription drugs and or over the counter medications while pregnant was 1525 (Table 1). Participants were also surveyed on what types of street drugs they used while pregnant. Many participants left the spaces blank while others answered 'yes' or 'no' to having used the street drug while pregnant. Out of the total sample, 1250 participants answered 'yes' to using one or more of the street drugs listed (Table 2.).

The one-way ANOVA between all the drug groups and the dependent variables from the KSADS revealed that for the most part there was no effect of maternal medication usage on a child's mental health outcomes with two important exceptions. There was an effect of maternal medication usage on suicidal ideation ($F(4,1797) = 2.554$, $p = .04$, Table 3.) Overall, two children out of the 296 in the perinatal antidepressant group stated that they were experiencing suicidal ideation. The other medication groups did not reveal any differences in suicidal ideation. There was also an effect of medication group for present suicide attempt, ($F(4,1795) = 2.398$, $p = .048$, Table 4.) Two children out of 296 in the perinatal antidepressant group stated that they had a present suicide attempt. Other reports of suicide attempts appear in one out of 135 of the perinatal opiates group and one out of the 'other' perinatal medication group with 613 participants.

In addition, we examined the change in KSADS mental health scores from baseline to year two and found that there was an increase in mental health diagnoses for every variable on the KSADS (smallest t (18302)=335.07, p<.001).

Discussion

We hypothesized that the offspring of childbearing people who took antidepressants during pregnancy would report more negative mental health issues in early adolescence compared to the offspring of childbearing people who did not take antidepressants during pregnancy. The data showed that there was no effect of maternal medication usage on the majority of the mental health measures on the KSADS in children aged nine to 12 years old.

When the medication groups and mental health outcomes were analyzed together, for the majority of the measures there was no effect of maternal perinatal medication use on their children's mental health with two important exceptions. We did find an effect of medication group that was specific to the participants who took antidepressants and their children's mental health outcomes measured at baseline in two of the measures on the KSADS. These variables were present suicide attempts and suicidal ideation. This is an important finding however, when we examined the number of suicide attempts at ages 9 and 10 there were two children in the antidepressant group reported present suicide attempts. In addition, there was one child in the opiate group and one child in the 'other' drug group also reported present suicide attempts. There were no differences found between these groups and the overall numbers endorsed in the sample were low. In addition, two children in the antidepressant group were also found to have

suicidal ideation. We examined these responses and found that they were from four different children for the two significant suicide relevant variables. If a child endorsed any suicide attempts and any reports of suicidal ideation the investigators were automatically contacted and appropriate assessments, interventions, and referrals were made. Regarding the current thesis study, there were no higher reports of suicide attempts in the perinatal antidepressant group compared to the other groups. It is important to recognize the seriousness of any number of children reporting a suicide attempt or suicidal ideation, but these reports are most likely not the result of the perinatal medication and may be a result of external or confounding variables. This may consist of the child's living environment and even extend to what the mother was doing or eating while pregnant.

There was also an attempt to examine the change in symptom and diagnosis report over time across medication groups using a repeated measures ANOVA and no significant effects were found for time or drug group. However, the low number of reported suicides attempts likely explains this finding. Overall, the hypothesis was not supported because there was no significant relationship between diagnosis and perinatal medication usage.

From the baseline KSADS diagnosis and symptoms report to the two year follow up there was an increase in diagnoses across the entire sample in every variable. However, it is difficult to tell how many children were displaying a new diagnosis compared to or in addition to existing mental health issues. This increase in mental health symptoms may be due to the onset of puberty in the

teenager participants. The onset of puberty typically occurs at age 8.0 to 14.9 years for females and from age 9.7 to 14.1 years for males (Lee, 1980). Onset of puberty is usually considered to coincide with the last major step in brain development which is the elimination of some 40% of neuronal synapses (Saugstad, 1989). The ABCD study did examine the effects of puberty but those data were not examined here. The onset of puberty brings an increase in hormones thus leading to fluctuations in mood thus causing the onset of mood disorders to begin around puberty (Saugstad, 1989).

Currently, doctors suggest terminating antidepressant usage while pregnant and there is evidence that discontinuing or continuing antidepressant use without dosage modification during pregnancy was associated with an increased risk of depression during the remaining gestational period (Bérard et al., 2019). Because of the gap in awareness and understanding that exists in the research area and the public realm, many people who give birth still suffer from depression and anxiety while pregnant which causes more severe and longer lasting changes in the child (Rahman, et al., 2007). If the child-carrier experiences depression while pregnant there is a greater chance their child will have a low birth weight (Rahman, et al., 2007). Low birth weight is a significant issue in developing countries and depression in the childbearing parent might be a valid screening method for potential low birth weight in a child (Kiess, et al., 2009). Currently, doctors and researchers have difficulty evaluating the evidence of whether patients should take antidepressants during the perinatal period for mood disorders because of the lack studies focusing on this issue.

There are positives and negatives to taking antidepressants during pregnancy. Untreated depression during pregnancy is a risk for the childbearing parent and the child because there is an increase in the risk of intrauterine growth restriction, low birth weight, and maternal-child relation disturbances (Dubovicky, et al., 2017). Some research has shown that treating depression during pregnancy and breastfeeding also represents a risk for the developing child because SSRI/ SNRI antidepressants can cross the placenta, the blood-brain barrier and pass into the milk, thus increasing the levels of monoamines in the brain which influences development (Dubovicky, et al., 2017). However, perinatal antidepressant usage did not have a significant effect on the child's development. The Dubovicky et al. findings show that perinatal antidepressant usage has no effect on a child's mental health at age 9 through 14. However, this study only examined newborns and animal models opening the discussion for perinatal antidepressant usage on adolescents.

Future research should examine differences between perinatal antidepressant usage and untreated perinatal depression. One can examine whether there is a difference in the child's mental health depending on whether the perinatal depression was treated or not. Current studies have shown that untreated depression can harm the child bearer, the fetus, and the newborn (Dubovicky, et al., 2017). These same studies have shown that treated depression during pregnancy and breastfeeding can also be a risk for the developing fetus and neonate because of the increase in level of monoamines caused by the SSRI/ SNRI antidepressants crossing the placenta, the blood-brain barrier and passing

into the milk (Dubovicky, et al., 2017). There are no studies weighing which is the lesser of the two evils: treated or untreated perinatal depression. It is an issue that pregnant people with mood disorders must consider for the health of their unborn child. Decisions regarding perinatal antidepressant usage must be made on a case-to-case basis.

In addition, studies examining depression and antidepressants during pregnancy should also measure S100B protein levels in-utero for untreated perinatal depression versus treated perinatal depression. Levels of S100B protein in the children at ages 10-14 years should be examined as well. This will allow researchers to investigate the lasting biological effects of perinatal antidepressant usage at a molecular level. However, there is the chance that these levels may not remain high for an entire decade. Examining S100B protein levels in infants may be the first step in this research.

Future clinical research is needed to help provide physicians and their patients with more accurate guidance on how to appropriately treat childbearing people during pregnancy with mood disorders to protect the health of the parent and child. By investigating mood in children whose birthing parent was prescribed antidepressants during pregnancy compared to those who were not will help determine if there are potential dangers to a child later in life. The goal is to eventually increase the safety surrounding physical and mental health during pregnancy for the childbearing person and their children.

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Tables:

Table 1. The total participants who have taken specified medication classes while pregnant. The opiate and stimulant drug classes only include pregnant people who took these medications as prescribed. Hormonal drugs include any kind of hormones. The other category is made of any drug that does not full under the other four categories which includes bipolar drugs. The reasons for taking these drugs were not included.

Drug (prescribed/over the counter)	**Total Users While Pregnant (n)**
Antidepressant	**304**
Opiate	**137**
Stimulant	**4**
Hormonal	**463**
Other	**617**

Table 2. The total participants that have taken one of the following street drugs listed (not prescription drugs) while pregnant.

Drug (Prescribed/over the counter)	Total User While Pregnant (n)
Tobacco	**620**
Alcohol	**315**
Marijuana	**245**
Cocaine/Crack	**51**
Heroin/Morphine	**19**

Table 3. Suicidal Ideation Active Intent Present. For the baseline assessment and the medication class there was a significant relationship for suicidal ideation active intent present ($F(4,1797) = 2.554$, $p=.04$.

Medication Class	**Suicidal Ideation Active Intent Present (0 = no or 1 = yes)**	**Frequency**	**Precent**
Antidepressants	**0**	**294**	**99.3**
	1	**2**	**0.7**
	Total	**296**	**100**

Table 4. Suicide Attempt Present. For the baseline assessment and the medication class there was a significant relationship for suicide attempt present ($F(4,1795) = 2.398$, $p=0.048$). Any medication class not included had no reports of suicide attempts.

Medication Class	Suicide Attempt Present (0 = no or 1 = yes)	Frequency	Precent
Antidepressants	**0**	**294**	**99.3**
	1	**2**	**0.7**
	Total	**296**	**100**
Opiates	**0**	**134**	**99.3**
	1	**1**	**0.7**
	Total	**135**	**100**
Other	**0**	**612**	**99.8**
	1	**1**	**0.2**
	Total	**613**	**100**

Table 5. The total number of participants indicating symptoms present on the KSADS during baseline and the 2 year follow up.

Diagnosis	Baseline (n)	Year 2 (n)
Bipolar I Disorder, current episode manic	**5**	**8**
Bipolar I Disorder, current episode depressed	**3**	**6**
Bipolar I Disorder, currently hypomanic	**2**	**1**
Bipolar I Disorder, most recent past episode manic	**49**	**157**
Bipolar I Disorder, most recent past episode depressed	**8**	**19**
Bipolar II Disorder, currently hypomanic	**2**	**1**
Bipolar II Disorder, currently depressed	**1**	**4**
Bipolar II Disorder, most recent past hypomanic	**21**	**45**
Unspecified Bipolar and Related Disorder, current	**10**	**22**
Unspecified Bipolar and Related Disorder, PAST	**111**	**127**
Major Depressive Disorder Present	**10**	**28**
Major Depressive Disorder, Current, in Partial Remission	**2**	**20**
Major Depressive Disorder, Past	**54**	**163**
Persistent Depressive Disorder (Dysthymia) PRESENT	**0**	**0**

Persistent Depressive Disorder (Dysthymia) In Partial Remission	**0**	**0**
Persistent Depressive Disorder (Dysthymia) PAST	**2**	**9**
Unspecified Depressive Disorder Current	**2**	**0**
Unspecified Depressive Disorder PAST	**49**	**158**
Generalized Anxiety Disorder Present	**7**	**36**
Generalized Anxiety Disorder Past	**6**	**53**
Suicidal ideation Passive Present	**23**	**54**
Suicidal ideation Active method Present	**8**	**29**
Suicidal ideation Active intent Present	**2**	**18**
Suicidal ideation Active plan Present	**7**	**11**
Interrupted Attempt Present	**0**	**3**
Aborted Attempt Present	**3**	**8**
Suicide Attempt Present	**3**	**7**
Interrupted Attempt Past	**2**	**3**
Suicide Attempt Past	**15**	**74**