

A systematic review and meta-analysis of the effects of SNPs in 5-HTTLPR, HTR1A, HTR2A and TPH-1 on response to SSRIs in depressed patients and its impact on adolescent and childhood depression studies

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Abstract

Depression is a serious illness that affects 20.9 million Americans a year. The most common method of treatment is selective serotonin reuptake inhibitors (SSRIs). Previous studies have shown that SSRI efficacy is limited. This review of current clinical data combined with statistical analyses has shown that the efficacy of SSRI treatment in adolescents is even more limited. It also has shown that the specific interactions between SSRIs and the serotonin transporter are still poorly understood.

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Introduction

Depression is a potentially debilitating condition that affects in a given year, 9.5 percent, or 20.9 million adults, of the American population. Depression can interfere with functioning and cause pain and suffering to a person and the people around them. The economic cost of treatment is very high and is not 100 percent successful. Many people respond to anti-depressant drug treatment differently; making it difficult to prescribe a drug for effective treatment. Some drugs have been shown to increase the risk of suicide, making it even harder for doctors to properly treat this illness [1].

Major depression (MDD) disorder, also called clinical or unipolar depression, is one type of depression. Dysthymia and bipolar depression are other types that commonly occur. Major depression affects 3 to 5 percent of children and adolescents in the United States and up to 15 percent of children at any given time have some symptoms of depression. Depression can have deleterious effects on growth and development, relationships and school performance. It is also the leading cause of youth suicidal behavior and suicide. More than 70 percent of children and adolescents with depressive disorders do not receive appropriate diagnosis or treatment. Misdiagnosis of MDD may be a result of child mental health training for health care professionals, inadequate number of child psychiatrists, and inequalities in health insurance. This makes childhood MDD an important and complex issue in our country today [2].

Suicide in children is rare, but risk of suicide increases after mid-adolescence to 15 per 100,000 in boys and 3 per 100,000 in girls, making depression the third leading cause of death in older adolescents. Suicidal ideation, a term used to describe the thought of committing suicide, is common in adolescents. Every year 19 percent of community dwelling adolescents have suicidal

ideation and approximately 9 percent commit suicide. The rates of suicidal ideation are even more common in adolescents receiving care for depression [3-5].

The efficacies of various anti-depressant medications for children and adolescents have been systematically studied and reviewed. Studies have shown treatment with serotonin reuptake inhibitors (SSRIs) has had limited effectiveness. Many publications have shown favorable risk/benefit profiles for some SSRIs, but some unpublished data has shifted the risk/benefit ratio toward unfavorable. One side effect of treatment with SSRIs is increased risk of suicide. To this day, adolescents have not been well represented in large observational and ecological studies of SSRI use on suicidal risk. This potential lack of generalizability of the literature to the adolescent population makes the efficacy of SSRIs very controversial, as no conclusive data have been found [6].

The genetic risk for suicide appears to be partly independent of risk for mental illness and other psychological stressors, as not all suicides have psychiatric illness at psychological autopsy. With continued progress in the study of the human genome and financially feasible procedures for genotyping, several candidate genes for the transmission of suicide risk have been identified, including the serotonin transporter (5-HTTL), the tryptophan hydroxylase (TPH), and the serotonin receptor types 1A and 2A (5HT1A, 5HT2A) genes that have been associated with suicidal behavior. The effects that these genes may have on impulsive behaviors, especially impulsive aggression, have only begun to be assessed; such links appear to be promising areas of future research, as they may be involved in possible mechanisms by which genetic risk can be estimate [7-9].

1.1 Depression and its Diagnosis

Prior to 1975, children and adolescents were thought to be incapable of experiencing depression, and clinical studies for younger populations were excluded from epidemiologic studies. After a meeting of the National Institute of Mental Health (NIMH), the existence and diagnosis of childhood depression became a clear problem in the general population. In the last two decades, the database for childhood disorders has grown immensely. Clinical studies from the United States and other countries have shown that the age of first onset of major depression is common in adolescents and young adults and that prepubertal onset, while less common, also does occur. It is now clear that adolescent depression is a chronic, recurring illness [10].

The diagnosis of major depression of children and adolescents comes from the same criteria used to diagnosis MDD

Table 1 General symptoms of depressive disorders

in adults. Two widely used classification systems for psychological disorders are the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)* and the *International Classification of Diseases (ICD-10)*. The main system used to diagnose younger populations is the DSM-IV. Five or more symptoms must be present nearly every day during the same two-week period to diagnosis an MDD. An MDD can be rated as mild, moderate, or severe; with or without psychotic symptoms; in full or partial remission[11].

Categories	Symptoms
Affective	Anxiety, anhedonia, melancholia, depressed or sad mood, irritable or cranky mood
Motivational	Loss of interest in daily activities, feeling of hopelessness and helplessness, suicidal thoughts, suicidal acts or attempts
Cognitive	Difficulty concentrating, feeling of worthlessness, sense of guilt, low self-esteem, negative self image, delusions or psychosis
Behavioral	Preference for time alone, easily angered or agitated, oppositional or defiant
Vegetative	Sleep disturbance, appetite change, lost or gained weight, energy loss, psychomotor agitation and retardation, lack of energy, decreased libido
Somatic	Physical or bodily complaints, frequent stomach aches and headaches

To classify a mood disorder as MDD, at least

one of the following symptoms must be present: depressed or irritable mood, or markedly

diminished interest or pleasure in all most all activities. The patient must show clinically significant impairment in social, occupational, or other important areas of functioning. A symptom that occurs from a direct physiological effect of substance abuse or a medical condition cannot be considered part of the diagnosis. An episode of major depression also cannot be superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or a psychotic disorder not otherwise specified [10, 12].

1.2 Epidemiology of Depression

Many questions about childhood and adolescent depression can only be answered by general population studies. “The epidemiologic data from large community survey in the United States on the incident of MDD among children and adolescents are sparse.”[11] This lack of data in the younger population is due in part to the previously held belief that MDDs were considered to only occur in adults, and that childhood and adolescent depression was a normal part of growth. The other controversy that arises in collecting data is over the means of assessing young people and who is the best informant, i.e., the child or the parent. Referral bias from clinical studies has also vitiated the use in describing patterns of diagnostic comorbidity or the sizes of impact of risk factors, or the level of need for services in epidemiologic studies [1].

Previously published epidemiologic studies have been limited to school districts in one community, or geographic areas, or have been conducted outside the United States. With the exception of a few studies, most samples of adolescents have been too small, i.e., under 1,000 and usually under 500.

Table 2: Definitions of depression adapted from DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 1996) [10]

DSM-IV criteria for a Major depressive disorder	ICD-10 criteria for a depressive disorder
<p>One or both of the following symptoms:</p> <ul style="list-style-type: none"> • depressed mood(in children and adolescents can be irritable mood) • markedly diminished interest or pleasure in almost all daily activities 	<p>In a typical depressive episode, the individual usually suffers from:</p> <ul style="list-style-type: none"> • depressed mood • loss of interest and enjoyment • reduced energy • increased fatigueability • diminished activity • marked tiredness after only slight effort
<p>Three or more of the following symptoms:</p> <ul style="list-style-type: none"> • significant weight loss or gain(of 5 percent per month) or decrease/increase in appetite (in children consider failure to make expected weight gains) • insomnia or hypersomnia • psychomotor agitation or retardation • fatigue or loss of energy • feelings of worthlessness, excessive guilt • poor concentration and indecisiveness • recurrent thoughts of death, suicidal ideation or suicide attempt 	<p>Other common symptoms are:</p> <ul style="list-style-type: none"> • reduced concentration and attention • reduced self-esteem and confidence • ideas of guilt and unworthiness • bleak and pessimistic views of the future • ideas or acts of self harm or suicide • disturbed sleep • diminished appetite
<p>Symptoms may be reported or observed.</p>	<p>Some of the above symptoms may be marked and develop characteristic features that are widely regarded as having special significance, for example the <i>somatic symptoms</i> that are listed below:</p> <ul style="list-style-type: none"> • loss of interest or pleasure in activities that are normally enjoyable • lack of emotional reactivity to normally pleasurable surroundings • waking in the morning two hours or more before the usual time • depression worsens in the morning • psychomotor retardation or agitation • marked loss of appetite or weight • marked loss of libido
<p>Symptoms have been present during the same two-week period nearly every day and represent a change from <u>previous functioning</u>.</p>	<p>Usually the somatic syndrome is not regarded as present unless at least four of these symptoms are present.</p>
<p>Symptoms cause clinically significant distress or impairment in social, occupational, educational or other important areas of functioning.</p>	<p>A duration of two weeks is required for a diagnosis of depression. The lowered mood varies little from day to day and is often unresponsive to circumstances and may show a <u>characteristic diurnal variation as the day goes on</u></p>
<p>Symptoms are not due to a mixed episode of mania and depression.</p>	<p>Atypical presentations are particularly common in adolescence. In some cases anxiety, distress and motor agitation may be more prominent at times than depression, and mood changes maybe marked by such features as irritability, excessive consumption of alcohol, histrionic behavior and exacerbation of pre-existing phobic or obsessional symptoms or by hypochondriacal preoccupations.</p>
<p>Symptoms are not due to the direct effects of a drug or general medical conditions such as hypothyroidism.</p>	
<p>The symptoms are not better accounted for by uncomplicated bereavement.</p>	

small sample size makes them unreliable estimates. The diagnostic methods and age groups in each study also vary greatly. The current lifetime prevalence rates of MDD from these studies have been estimated to be about five percent. The similarity of lifetime rates between younger groups and adults suggests that a large percentage of subjects with major depression have onset while young [11].

The most comprehensive data for adults comes from the National Comorbidity Survey (NCS). The NCS is a nationally representative sample of over 8,000 people from U.S. households ages 15 to 54. Although only 600 people in the survey were under the age of 18, the rates from the U.S. population are consistent with published adolescent data. The lifetime prevalence of MMD for 15 to 18 year olds was about 14 percent. An additional 11 percent were estimated to have a lifetime of minor depression, with a higher rate among females than among males. While the sample did not survey children under 15, subjects were young enough to conduct retrospective studies [13].

The information from the retrospective studies show reasonably valid information regarding the age of first onset of MDD in childhood or adolescence. The Kaplan-Meier age-at-onset curves for major and minor depression from the NCS survey show that meaningful risk begins in the early teens and continues to rise in a roughly linear fashion within cohorts through the 20's. The shapes of these curves are very similar to onset curves reported in other epidemiologic studies of adolescent depression. The data from this survey present relatively strong evidence that the first onset of MDD frequently occurs in adolescence, and in some cases early childhood. The NCS also showed that the rates of MDD, especially in young people, have been increasing [11, 13].

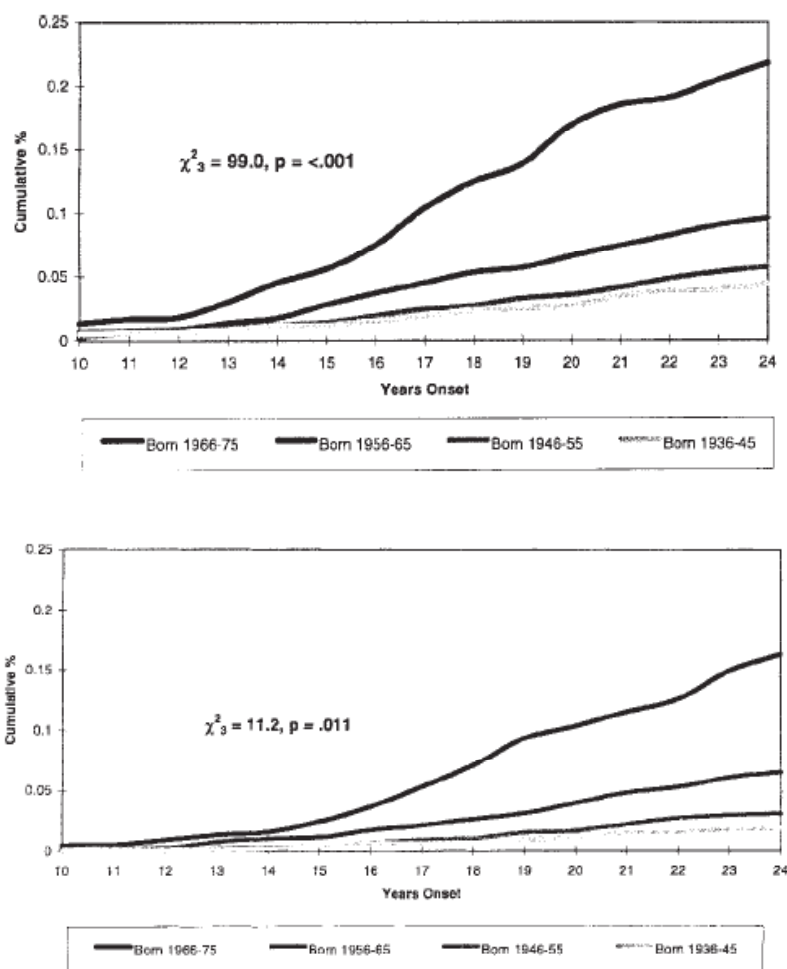


Figure 1. Kaplan- Meier cumulative lifetime prevalence curves for major and minor depression in the total NCS survey by cohort. Both curves show that meaningful risks for depression begins in the early teens and continues to rise roughly linearly with groups of cohorts throughout their 20's. The shape of these curves are similar to that of onset curves reported in other studies of adolescent depression. These curves also show that substantial prevalence increases in cohorts born after the 1960's [13].

The presence of comorbidities is another issue with adolescent and childhood depression. Comorbidity is the presence of another illness in addition to the primary disease or disorder. In depressed adults and youths, comorbidity with other psychiatric issues is a rule. The most common disorder is an anxiety disorder. Over 60 percent of depressed adolescents have a history

of an anxiety disorder. A common pattern of onset includes an anxiety disorder before puberty, particularly phobias, with the emergence of major depression in adolescents. Disruptive behavior disorders are also common before puberty. Substance abuse in the latter stages of adolescence with MDD is also common. Unfortunately, the effects of comorbidities in adolescence have not been well studied [14].

The risk factors for adolescent MDD have been identified by both epidemiologic and clinical studies. Many studies have shown that low socioeconomic status, high life stress, sexual abuse, physical illness, low academic achievement, depressive cognitions, low self-esteem and various measures of family disruption are associated with the presence of psychiatric disorders. Each study has shown a slightly different pattern of effect each factor has had on a disorder. Despite this abundance of information, no pattern of risk factors has consistently appeared to be associated with depression, except for the changes that occur at puberty. This lack of consistency across the literature may result from the inability to properly measure these potential risk factors [2].

1.3 Treatment of Depression

An MDD is one of the most common psychiatric disorders seen in the community and outpatient settings. Substantial evidence has supported three manual-based psychotherapies have been used to successfully treat MDD cases. These therapies are cognitive therapy, behavior therapy and interpersonal therapy. Two other forms of psychotherapy have also been implemented in treatment for MDD, but have had less success. These two are brief dynamic therapy and problem-solving therapy [11].

The first kind of therapy, cognitive therapy, is the most widely studied psychotherapy for MDD. Cognitive therapeutic treatment is based on the model that cognitions of depressed

individuals are negatively biased. These negative cognitions are one factor that play a role in the initiation and maintenance of depressive disorders. Cognitive therapy also involves the application of both behavioral and cognitive techniques. Behavioral techniques serve to engage the patient in activities that give them pleasure, while cognitive techniques help the patient recognize negative cognitions and to evaluate the veracity of their beliefs [15, 16].

Behavioral treatment, another common therapy, is based on the model of Lewinsohn and MacPhillamy's approach to treating MDD. The primary goal of this model is to increase the frequency of pleasant activities in a patient's life. The largest study of behavior therapy for MDD found that it to be better than psychotherapy, relaxation therapy, and medication. As with cognitive therapy, there is evidence that behavior therapy is efficacious but not a unique effective, acute treatment for MDD [17-19].

The third widely used psychotherapy for depression is called interpersonal therapy (IPT). In interpersonal therapy, the interpersonal problem that triggered the current depressive disorder is addressed and the patient is helped to build communication and interaction skills to resolve it. This model of treatment assumes that although depression is caused by a number of factors (genetic, biological, social) interacting in complex ways, it is usually triggered by problems in the four interpersonal domains: role transition, grief, interpersonal deficits, and interpersonal disputes. Several studies have supported the efficacy of IPT for acute treatment of MDD in adults seeking treatment in psychiatric and primary care settings [20-27].

Brief dynamic therapy is a less well-studied psychotherapy. The brief version of dynamic therapy typically has a clear interpersonal or intrapsychic focus. It utilizes therapist interpretations as the key intervention designed to increase self-understanding about interpersonal or intrapsychic issues that may be contributing to MDD symptoms. Manual based

brief dynamic therapy in MDD has been evaluated in several studies. Although it appears to be a promising possibility for the acute treatment of MDD, more data on comparisons to credible control groups are needed. The other less studied therapy is problem-solving therapy. It has been examined in the treatment of MDD by several controlled studies. Different results have been determined in each study. It appears that it may also be an acute treatment for MDD. Additional larger studies are needed, as are comparisons to other standard therapies for MDD [28-30].

Drug treatment is another therapy used for MDD. In adults, effective antidepressants for the treatment of MDD include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and dual-action agents. While partial symptomatic response is usually achieved using drug treatment, complete remission is often hard to obtain. While incomplete remission is a clinical issue, the existence of residual symptoms may be the best predictor for a relapse or recurrence; which may have very significant implications if the first episode of MDD occurs in adolescence. Therefore, the determination of the psychopharmacological approaches, either monotherapies or combinations, that have the best outcomes in adults may be significant for the treatment of adolescent and childhood depression [24].

The older class of antidepressants used to treat adult MDD inhibit different combinations of serotonin, noradrenergic, and dopamine receptors. These drugs include tricyclic and heterocyclic antidepressants: amitriptyline, amoxapine, clomipramine, despiramine, doxepin, imipramine, maprotiline, nortriptyline and protriptyline. Their antagonistic effects at other receptor sites can result in unpleasant side effects. The MAOIs, another older class of drugs, irreversibly inhibit monoamine oxidase isozymes forms A and B. While not fully understood, it is thought that the blockade of isozyme A gives these drugs their clinical efficacy. One major

issue with this class of antidepressant drugs is the required tyramine-restricted diet. If this diet is not followed, the effects can be fatal. Also the usage of other drugs that increase synaptic monoamines in combination with MOAIs must be avoided [11].

The newest generation of antidepressants is considered to be dual action drugs. They are the selective serotonin and nonadrenaline reuptake inhibitors (SNRIs). These inhibitors include venlafaxine (Effexor), duloxetine (Cymbalta), and milnaciprane. The dual reuptake inhibition may contribute to the high rates of remission of depressive symptoms compared to those with SSRIs. Although these drugs have great promise, there are still issues that have to be worked out with SNRIs[11].

Currently, the most common and first line of medical treatment for adult MDD are SSRIs and include fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Clexea), and esitalopram (Lexapro). These drugs have a greater affinity for the serotonin transporter than for the nonadrenergic transporter. Each compound selectively inhibits 5-hydroxytryptamine (5-HT) reuptake and has unique secondary binding properties. While the main mechanism of action for each of these compounds is similar, differences in clinical criteria for their application exist. The most important clinical factor in deciding which SSRI to administer is its elimination half-life[31].

There are four main advantages of SSRIs over older antidepressant drugs with the first being side effects. They have a more benign tolerability profile with fewer adverse side effects than other types of drugs. Most of the adverse effects of SSRIs are mild and do not last very long. The second advantage is in drug administration since they are easier to administer because they require little to no dose titration, as opposed to older drugs that do require titration in administration. Unlike other antidepressant drugs, they can be routinely given once daily. Third,

SSRIs have been shown to be involved in fewer drug interactions, especially drugs of serious nature like sedatives, sympathomimetics, alcohol and antiarrhythmics. The fourth advantage of these drugs is that they are better tolerated in overdose than other antidepressant drugs [32].

Pharmacological treatment for adolescents with MDD is a current issue in clinical studies. The treatment for younger groups differs from drug treatment for adults with MDD. This differential treatment is the result of evidence from pediatric MDD trials that suggest that antidepressants are only modestly efficacious. Another significant finding from these studies of pediatric MDD was that drug treatment for adolescents slightly increased the risk for suicidal ideation and suicide. This issue is complex, as the clinical data available neither support nor refute these treatment concerns for pediatric MDD [6, 14].

To date, the only clinical studies that have had success in treating MDD in adolescents have been double blind, placebo controlled trials using SSRIs. Controlled large-scale studies demonstrating the efficacy of antidepressants in the treatment of youths with MDD are limited to acute SSRI trials. Moreover, it has not been determined from these trials whether children and adolescents respond to SSRIs similarly. At this time there are no data available that support the efficacy of other classes of antidepressants in treating youths with MDD. An even smaller amount of information exists that describe the optimal treatment duration and there is little known about the long-term safety of antidepressants in children [11].

1.4 Molecular basis for depression and its suicidality

As mentioned previously, suicide is a negative side effect of SSRI treatment in adolescence . It is the third leading cause of death in older adolescents, making this association a serious issue for both depressed youth and primary care physicians. An association between genotype and vulnerability to major depressive disorder has long been suspected on the basis of

family and twin studies. A meta-analysis of findings from twin studies estimated MDD's heritability to be 0.33 (confidence interval, 0.26-0.39). Heritability is a measure of the percentage of the variance of the trait that is due to genetic factors in a specific population, and it also does not assume any gene-environment interaction. In families with increased prevalence of MDD, the risk of developing the disorder was greater in those members exposed to a highly stressful environment. At this point in time, the genes of highest interest in the study of vulnerability to depression are those involved in the synthesis and actions of serotonin. These genes of interest include the tryptophan hydroxylase (TPH), HTR1A, HTR2A, and serotonin transporter genes [33, 34].

A serotonergic gene that has been studied in relation to suicide is the HTR2A receptor gene that has a single nucleotide polymorphism (SNP) on chromosome 13q14.1–14.2. This particular SNP has been labeled T102C. The possibility of a role of this gene in the etiology of suicide has arisen primarily due to findings that suggest abnormalities in HTR2A receptors on cell surfaces in suicide cases. The polymorphism, however, does not appear to have a functional relationship with the receptor. A previous study reported no association between genotype of the T102C polymorphism and HTR2A receptor density. Therefore, it is not surprising that most studies report little, if any, relationship between the T102C polymorphism and suicidality [35, 36].

A second serotonin gene, the tryptophan hydroxylase gene (TPH-1), is responsible for the production of TPH, the rate-limiting enzyme in the synthesis of serotonin. This central role makes it an obvious target of suicide studies. The gene is located on chromosome 11q7, and two polymorphisms have been the subject of several investigations, namely A218C and A779C. A recent meta-analysis found that the presence of the 218A allele was significantly related to

increased risk for suicide. In other studies, there has been no consistent relationship between the A779C polymorphism and suicide [37-40].

In one investigation of suicidality in violent male offenders, Nielsen and colleagues classified offenses as impulsive or non-impulsive. Suicidal impulsive offenders had a higher likelihood of carrying the 779C allele, but suicidal non-impulsive offenders were less likely to carry this allele. Research findings document close linkage of the A218C and the A779C polymorphism insofar as individuals have the same genotype for both the A218C and the A779C polymorphisms, suggesting that the results regarding the A218C polymorphism should hold true for the A779C polymorphism as well. Mann notes that the “implications of these results are unclear, given that these two polymorphisms do not seem to have any functional influence on TPH gene transcription.” It is clear that the mechanisms of the TPH gene's influence on suicidality and its potential effect of impulsivity need further study [38, 40].

The third gene involved in serotonergic function that is a subject of suicide study is the serotonin transporter gene (SERT) that moderates the availability of serotonin in the synaptic cleft. The gene is located on chromosome 17q12. A polymorphism in the transcriptional control region of this gene (“promoter”, 5-HTTLPR) consists of a 44 base pair insertion or deletion. Two alleles have been called the long (*l*) and short, or stress sensitive, form (*s*). To date, studies examining the relationship between the *s/s*, *s/l* and *l/l* genotypes and suicidality have shown mixed results. One study that followed 103 suicide attempters over a year found that the presence of the “*s*” allele increased the risk for subsequent suicide attempt. Furthermore, the frequency of the *s/s* genotype rose as the number of suicide attempts rose. Also, subjects with the *s/s* genotype had significantly higher scores on a measure of impulsivity [9, 41].

Joiner and colleagues reported that individuals with a family history of suicide were more likely to carry the s/s genotype than were those without a family history. In a postmortem study of suicides, Mann et al. found that short alleles were more common among suicide victims than among others, although this relationship was not statistically significant. An emerging area of research is that of impulsivity and aggression and differential expression of these behaviors across SERT genotypes as the potential link between impulsivity and suicide warrants further investigation [42, 43].

Functional polymorphisms in the promoter region of the serotonin transporter gene were first associated with differential expression of depressive symptoms and emotional or personality behaviors such as neuroticism in humans by Lesch et al. in 505 subjects representing male sibling, other family members, and volunteers. These investigators noted that population associations between a genetic marker and a phenotypic trait can arise from population stratification or from genetic transmission. Because these sibling pairs are by definition ethnically and racially homogeneous, any difference in trait scores between genetically discordant sibs must reflect true genetic transmission. The Lesch study, using within-pedigree analysis, demonstrated that the observed associations between SERT genotype and personality were the result of genetic transmission rather than population stratification [41].

In a study of the interaction of stressful life events with the SERT gene that moderates pathways from stress to depression in young adults, Caspi et al. reported that a variant of the serotonin transporter gene doubled the risk of depression following life stresses in early adulthood. In their prospective-longitudinal cohort study, Caspi, Sudgen, Moffitt and colleagues examined why stressful life events led to depression in some people but not in others. The

Dunedin Birth Cohort used in the Caspi study consists of 1,037 children, of whom 52% are male and who were assessed at ages 3, 5, 7, 9, 11, 13, 15, 18, and 21[44].

For the gene by environment study, 847 of the 1,037 Caucasian non-Maori New Zealanders were divided into three groups on the basis of their genotype for a variation in SERT: s/s, s/l (l/s) and l/l. There was no difference in genotype frequencies between the sexes. Stressful life events occurring after the 21st birthday and before the 26th birthday were assessed with the aid of a life-history calendar, a highly reliable method for ascertaining life event histories. Thirty percent of the study members experienced no stressful life events, 25% experienced one event, 20% two events, 11% three events, and 15% four or more events [44].

There were no significant differences among the three genotype groups in the number of life events they experienced, suggesting that the serotonin transporter genotype did not influence exposure to stressful life events. In a hierarchical logistic regression model, the main effect of genotype was not significant, the main effect of number of life events was significant, and the interaction between genotype and number of life events was significant for depression symptoms, MDD, and suicidal ideation. These patterns tracked informant reports of depression. Caspi et al. concluded that their study provided evidence of a gene-by-environment interaction, in which an individual's response to environmental insults “germs” is moderated by genetic makeup [45].

In a replication study in adolescents of the findings of Caspi et al., Kaufman reported that measures of the quality and availability of social supports were found to mediate risk for depression associated with a history of maltreatment and the presence of the short (s) allele of the serotonin transporter gene promoter polymorphism (5-HTTLPR). This adolescent replication study extends the finding to children and demonstrates the ability of social supports to further

mediate risk for depression. Children with the s/s genotype, a history of maltreatment and no positive supports had depression scores twice as high as the non-maltreated comparison children with the same genotype [46].

The presence of positive supports mitigated the apparent effects of maltreatment and the s/s genotype to the extent that that maltreated children with this profile had only minimal increases in depression scores. A particularly intriguing result of the Kaufman study is the observation of a main effect of SERT genotype on depression scores that was not observed in the Caspi study or any of the subsequent adult replication studies as far as we know. In the Kaufman study, adolescents with the s/s genotype had Mood and Feeling Questionnaire depression scores of 20.6 (SD=12.4) compared to mean scores of 12.7 (SD=7.7) for comparable adolescents with the l/l genotype (chi-sq=12.3, p=0.002). Interestingly, the mean age of the Kaufman cohort was 10 years with a range of 5-15. As such, it is likely that the vast majority of these children were experiencing their first episode of MDD. Kovacs reports that there is “impressive” evidence that children and adolescents with MDD represent almost entirely first-episode probands. In seven studies reviewed by Kovacs, 90 to 100 percent of the children and adolescents diagnosed with MDD were in their first episodes. It is now known that episodes of depression are associated with a reduction in the size of the hippocampal region in the brain and neuronal insult. There is evidence that the effects of these insults are cumulative over recurrent episodes of depression [47-49].

Other SERT replication studies have demonstrated an association between genetic variation in the promoter region of the serotonin transporter and unipolar depression in adults, [50], [51] as well as pediatric populations. A recent meta-analysis summarizing the relationship between SERT and depressive disorders reported mixed results, with an association observed

between SERT and bipolar disorder, but not unipolar depression. The unipolar analysis, however, was limited to 14 case control designs, none of which included pediatric populations. The meta-analysis that was received in the summer of 2003, however, predated Nobile's case control replication study in children that reported an association of the "s" allele of SERT with MDD [34-36, 52].

In sum, the relationships among genetic susceptibility, environmental risk and mood disorders are illustrated in figure 2 for individuals with the stress sensitive form of SERT, labeled as s/s or s/l genotype as well as those with a l/l genotype that does not appear to confer increased risk for depression due to stress. The likelihood of mood disorders is greatest when both risk from genetic background and environment are high. Individuals carrying the stress sensitive SERT allele are hypothesized to be at greater risk for mood and anxiety disorders at a given level of risk from genetic background and environmental stress than are individuals with the long or stress resistant allele. Consistent with empirical evidence that the stress resistant allele does not prevent disease in the context of high risk from the environment [50].

To date ten studies have been completed that examined the influence of SERT polymorphisms on the effects of SSRIs in depressed patients. These studies suggest that depressed Caucasian adult patients carrying the "s" allele are at increased risk for more mood symptoms and have poorer outcomes to SSRI treatment than l/l carriers. These findings suggest evidence of differential outcomes of SSRI treatment. From a review of the ten studies, findings about the influence of SERT polymorphism on SSRI treatment outcome were variable for Asian populations and based on two studies. However, if confirmed, these findings would indicate that ethnicity could be important in the effect of SSRI treatment in patients with MDD [37, 38].

A study by Murphy et al. [53] investigated differences in function between the long and short polymorphisms in the promoter region of the serotonin transporter gene because previous

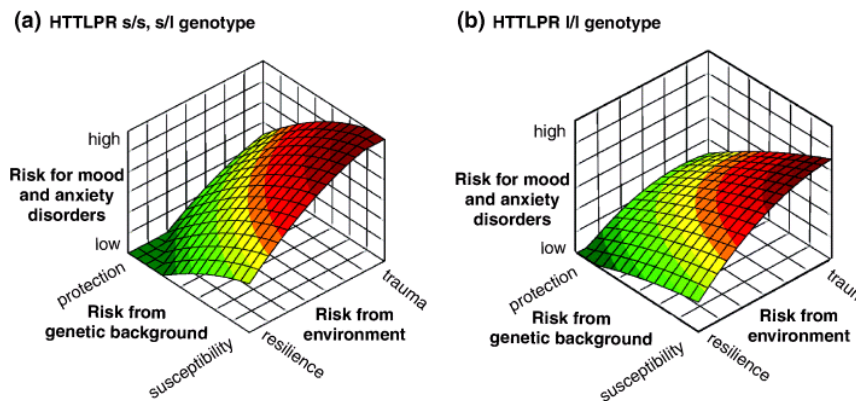


Figure 2 The serotonin transporter gene-linked polymorphism and negative emotionality, Environment. *Genes, Brain and Behavior* (2003) 2: 332–33.

reports had identified an association between the “s” allele and decreased efficacy of selective serotonin reuptake inhibitors. They randomized 246 cognitively intact patients aged 65 years or older with MDD to either mirtazapine (an SNRI, i.e., a mixed noradrenergic and serotonergic antidepressant) or the SSRI paroxetine. Patients with the “s” allele treated with paroxetine showed a small impairment in antidepressant response. Among mirtazapine-treated patients, there was little indication that the promoter polymorphism affected antidepressant efficacy; however, the promoter polymorphism had a dramatic effect on adverse events. Among paroxetine-treated patients, “s” allele carriers experienced significantly more severe adverse events, achieved significantly lower final daily doses, and had more discontinuations due to adverse events. Mirtazapine-treated patients had the opposite finding: “s” allele carriers had significantly fewer discontinuations due to adverse events, experienced less severe adverse events, and achieved higher final daily doses. Murphy concluded that the S allele of the SLC6A4 promoter polymorphism is associated with a poor outcome after treatment with selective serotonin reuptake inhibitors [53].

Yu et al. tested the hypothesis that SERT polymorphism is associated with SSRI antidepressant response by evaluating total and cluster depressive symptoms in 121 Chinese patients diagnosed with MDD. Findings revealed that patients with the l/l genotype had a significantly better response to fluoxetine when compared to the “s” allele carriers on the basis of total ($p = 0.013$), core ($p = 0.011$), psychic anxiety ($p = 0.005$), and somatic anxiety ($p = 0.002$) symptoms of the Hamilton Depression Rating Scale-score percentage change [42].

Recently published findings of a randomized trial conducted in 81 Japanese patients compared the effects of two currently used SSRIs by SERT genotype. Clinical responses to paroxetine and fluvoxamine were evaluated for patients with MDD. Patients with the l/l genotype had a greater percentage reduction on the total score ($p=0.06$) and somatic anxiety items ($p=0.026$) on the Hamilton Depression Rating Scale score compared to s/s genotype carriers. Paroxetine was significantly more effective than fluvoxamine in the s/s carriers, as evaluated on the percentage reduction in total score ($p=0.012$) and core ($p=0.049$) HAM-D after 4 weeks of medication, but not in the l/s carriers. Kato's concludes that a genetic test may be useful in investigating the efficacy of the two SSRIs, and that normalization by the 5HTTLPR genotypes may lead to improvement of the precision of comparative analysis. As far as we are aware, no past studies have examined SSRI treatment response or treatment emergent side effects for adolescent MDD, a gap that would be addressed by the current investigation [54].

Pharmacogenetic studies have demonstrated an association with SERT polymorphism and poorer outcomes of selective serotonin reuptake inhibitors (SSRI) treatment among depressed Caucasians with the stress sensitive form of SERT. Yoshida et al. studied depressed Japanese patients but reported association between the short allele and more favorable treatment response, suggesting possible racial and ethnic variation in the moderating effects of SERT. At

present there are no studies that have examined the relative importance of variations in the SERT gene and treatment outcomes in depressed adolescents nor variation in treatment side-effects, particularly suicidality, across SERT genotypes. Furthermore, we do not know what effect treatment has on the likelihood of first recurrence of major depression and the role of genetic vulnerability in its recurrence [55].

2. Methodology

2.1 Data Collection

In order to assess which genotypes may have an influence on response to SSRI treatment, data pertaining to response rates by genotype for specific genes were pooled from the most relevant articles. To obtain these articles, pubmed.gov was accessed online. Pubmed is an electronic database of biomedical research articles from the 1950's on. The database was accessed on 10/24/2006 and the following terms we entered into the search field: polymorphism OR genetic variant OR SNP OR single nucleotide polymorphism) AND (serotonin OR serotonin transporter OR SERT OR 5HTT OR 5HTTLPR OR tryptophan hydroxylase OR serotonin receptor OR monoamine oxidase OR MAO OR MAOI OR monoamine oxidase receptor OR MAO receptor) AND treatment response OR treatment failure OR treatment outcome OR refractory. The search was limited to the last 3 years from the date of access.

Once the publications list was returned, the inclusion criteria were defined. In order to obtain data that dealt solely with MDD, all studies that involved more than one psychiatric disorder were excluded. Since the focus of this study is response to SSRI treatment, all studies that investigated another treatment were excluded. The depression score rating systems were all scaled differently, so there was no method for determining a substantial change in scores after SSRI treatment. The genes that were identified in the publications and used for this study were: the promoter region of the serotonin transporter gene (5HTTLPR), the tryptophan hydroxylase gene (TPH-1), and the serotonin type 1A and 2A receptor genes.

2.2 Meta Analyses of candidate Genes

In order to estimate the effects of the various SNPs on response to SSRIs as defined by all included studies as a relative decrease on the Hamilton Depression rating scale (HAM-D)

score, a meta-analysis was performed for each SNP. The HAM-D is a 21-question multiple-choice questionnaire which doctors may use to rate the severity of a patient's depression. A response rate ratio comparing those with and without the allele of interest was calculated for each gene via meta-analysis. Study heterogeneity was assessed by a χ^2 test with a level of significance set at 0.05. A sensitivity analysis for each gene was conducted using Stata 9.

All statistical analyses were performed in Stata 9, and assumed a random effects model. Throughout the analysis, the DerSimonian and Laird estimate of variance from inverse variance weighted methods was used to calculate the pooled risk difference from the raw data of each study. Additionally, the authors decided to use unstandardized differences to compare the groups. In order to estimate the effects of the various SNPs on response to SSRIs as defined by all included studies as a decrease increase on the HAMD score, a meta-analysis was performed for each SNP.

3. Results and Discussion

3.1 Data collection and organization

The search of the Pubmed database returned 106 results. Of those 106 publications, 22 fit the inclusion criteria and were selected for further data analysis. Of these 22 publications, no studies were done on SSRI treatment in children and adolescents. Although the literature lacked data on children and adolescents, the authors feel that the adult data will be generalizable to a younger population because genes will likely have a similar effect at both younger and older ages. For each study, the gene(s) being studied were identified along with the SSRI(s) being administered to the patients. Ethnicity was also noted as it has been shown in the literature to affect treatment outcomes in genetic studies [56].

Table 3 shows the papers included in this study. In the data searching process, it was noted that no studies had been done on children or adolescents. This is a serious concern that has been addressed in the literature review section. The lack of data from younger populations makes it hard to determine proper treatment of MDD at first onset. Since no pediatric data could be collected, the statistical analyses were performed on the clinical data from adult studies. The authors feel that these results from older populations will be generalizable to children and adolescent populations.

Table 3. Publications included in the study of SNP in genes known to affect treatment of MDD with SSRIs.

Name	Year	Gene studied	Drug(s)	Ethnicity	Sample Size
Kim et al.	2006	5HTTLPR	fluoxetine, sertraline	Korean	136
Ham et al.	2006	TPH-1	citalopram	Korean	105
Kato et al.	2006	5HTTLPR, HTR2A, HTR3A, HTR3B	praxetine, fluvoxamine	Japanese	100
McMahon et al.	2006	HTR2A	citalopram	American	4,041
Hong et al.	2006	5HTTLPR	sertraline	Chinese	45
Yu et al.	2005	HTR1A	fluoxetine	Chinese	222
Arias et al.	2006	COMT	fluvoxamine, citalopram, paroxetine	European	346
Choi et al.	2005	HTR2A	citalopram	Korean	71
Lee et al.	2005	5HT6	multiple SSRIs	Korean	127
Murphy et al.	2004	5HTTLPR	paroxetine	American	246
Tsai et al.	2004	5HT1B	fluoxetine	Chinese	160
Arias et al.	2003	5HTTLPR	citalopram	Spanish	131
Ham et al.	2005	TPH-1	multiple SSRIs	Korean	93
Hong et al.	2006	5HTTLPR, HTR1A, HTR2A, TPH-1, GBN3	fluoxetine	Chinese	224
Joyce et al.	2004	5HTTLPR	fluoxetine	N/A	195
Kirchnheiner et al.	2006	DAT-1	multiple SSRIs	Northern European	1,910
Lee et al.	2004	5HTTLPR	multiple SSRIs	Korean	128
Parsey et al.	2006	HTR1A	N/A	N/A	22
Perlis et al.	2003	5HTTLPR	fluoxetine	American	36
Perna et al.	2005	5HTTLPR	paroxetine	Italian	92
Peters et al.	2004	HTR1A, HTR2A, HTR2C, MAOH, SLC6A4, TPH-1, TPH-2	fluoxetine	American	96
Serretti et al.	2004	5HTTLPR, TPH-1	multiple SSRIs	Italy	185

3.2 Meta analysis of the 5-HTTLPR gene

In order to assess treatment responses for certain genotypes, response rate ratios were computed and a meta analysis was performed on each gene of interest. A response rate ratio is the “risk” of response to SSRI treatment relative to an exposure; it is the probability of an event occurring in an exposed group versus the control group. If the number of responders and non-responders to treatment for a specific genotype are given, then the authors were able to calculate response rate ratios. For the promoter region of the SERT gene (5-HTTLPR) there were three genotypes of interest (l/l, l/s, and s/s). To examine the relative effect of SSRI treatment in the s/s homozygote, the s/l and l/l patient responses were collapsed into one category, since previous studies have shown that s/s carriers have a higher risk of suicide.

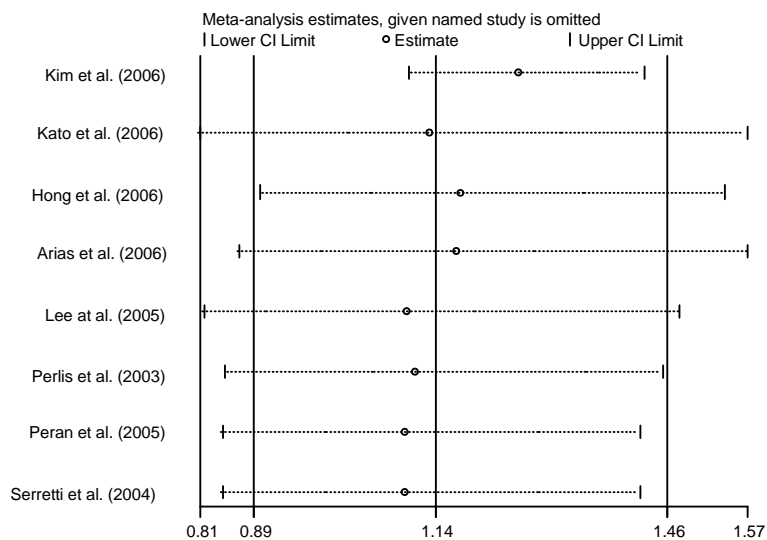
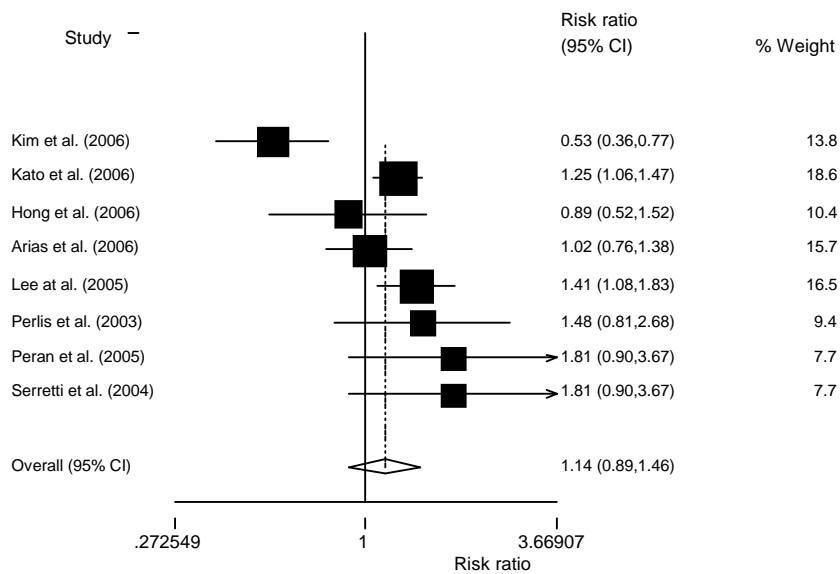
Table 4. Number of responders and nonresponders for 5-HTTLPR meta analysis

Study	# responders (l/l & l/s)	# non-responders (l/l & l/s)	# responders (s/s)	# non-responders (s/s)
Kim et al. (2006)	19	30	55	20
Kato et al. (2006)	30	1	38	11
Hong et al. (2006)	12	9	9	5
Arias et al. (2006)	71	33	18	9
Lee at al. (2005)	22	6	53	42
Perlis et al. (2003)	044	62	9	23
Peran et al. (2005)	48	92	7	30
Serretti et al. (2004)	48	92	7	30

The meta analysis of the response rate ratios for the 5-HTTLPR gene resulted in a response rate ratio of 1.14 (95% CI: 0.89 to 1.46), indicating that there was no statistically significant different response rate between the s/s and l/l combined with s/l genotypes. However, a test for heterogeneity yielded chi-squared value of $X^2 = 24.81$, and a p value of 0.001, indicating that there was a significant amount of heterogeneity present among the studies. This analysis indicates that the treatment with SSRIs has no differential effect on different genotypes;

meaning the response in these studies was not statistically significantly different between the l/l combined with l/s and the s/s genotypes. The sensitivity analysis shows that the overall response rate ratio would be increased in magnitude and precision if the Kim e al. (2006) was removed from the analysis, indicating a high weight placed on this study.

Figure 3. Forest plot from the 5HTTLPR meta analysis and sensitivity analysis plot



3.3 Meta analysis of the TPH-1 gene

The meta-analysis of the TPH-1 gene showed similar results to that of the 5-HTTLPR. In this study, the response rates were calculated for the A/A, A/C and C/C genotypes. Some previous studies have shown that A218C has had an effect on suicidality, while others have shown no effect. Since there was apparent disagreement in the literature, all possible response rate ratios of genetic combinations were subject to meta analysis and then analyzed. In all 5 meta-analyses, the p value testing the null hypothesis that the response rate ratio was equal to 1 was higher than 0.05, indicating that none of the comparisons demonstrated a statistically significant difference between genotypes in response to SSRIs. The individual sensitivity analyses show that the data are in fact robust upon removal of each study. These data provide statistical evidence that there is no difference in response to treatment between the different genotypes of TPH-1.

Table 5. Number of responders and nonresponders for TPH-1 meta analysis

Study	# responders (A/A)	# nonresponders (A/A)	# responders (A/C)	# nonresponders (A/C)	# responders (C/C)	# nonresponders (C/C)
Ham et al. (2006)	16	16	29	23	16	5
Ham e al. (2005)	13	4	35	11	23	7
Serretti et al.(2004)	11	23	24	57	20	39

Figure 4. Forest plot from the TPH-1 (A/A vs. A/C) meta analysis and sensitivity analysis plot

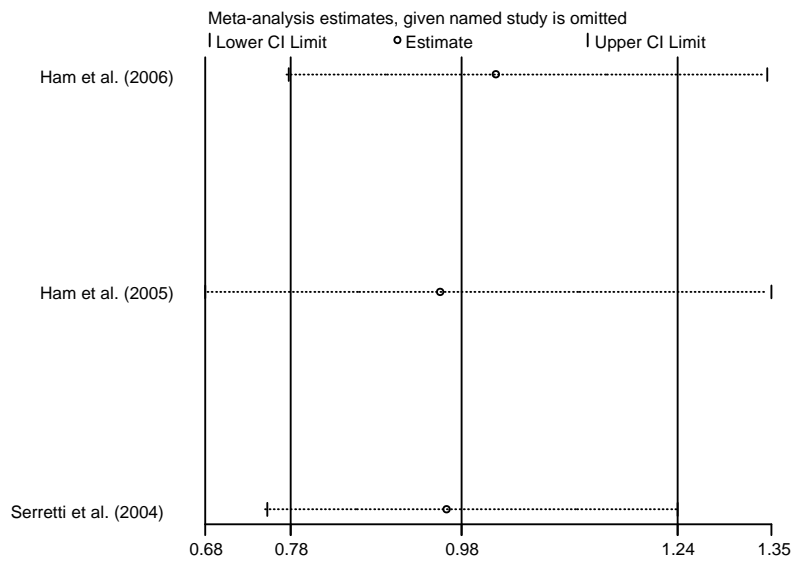
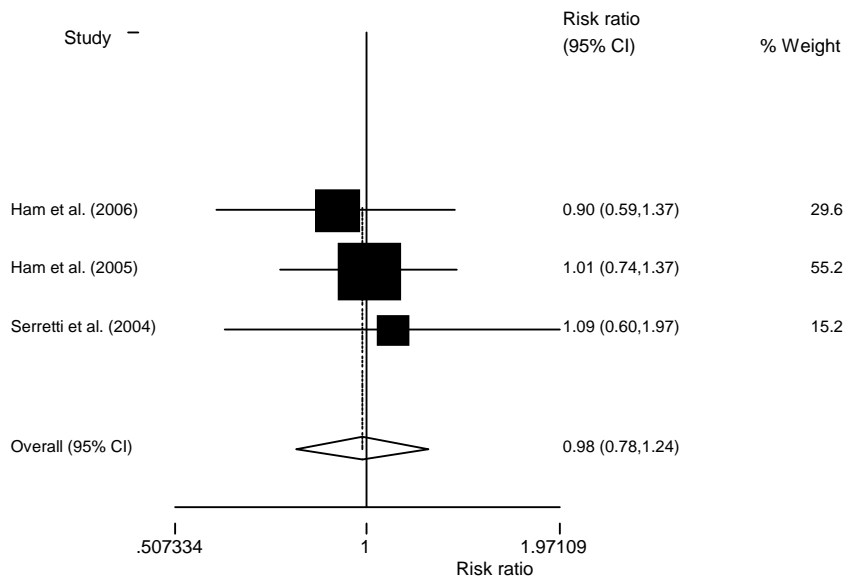


Figure 5. Forest plot from the TPH-1 (A/A and A/C vs. C/C) meta analysis and sensitivity analysis plot

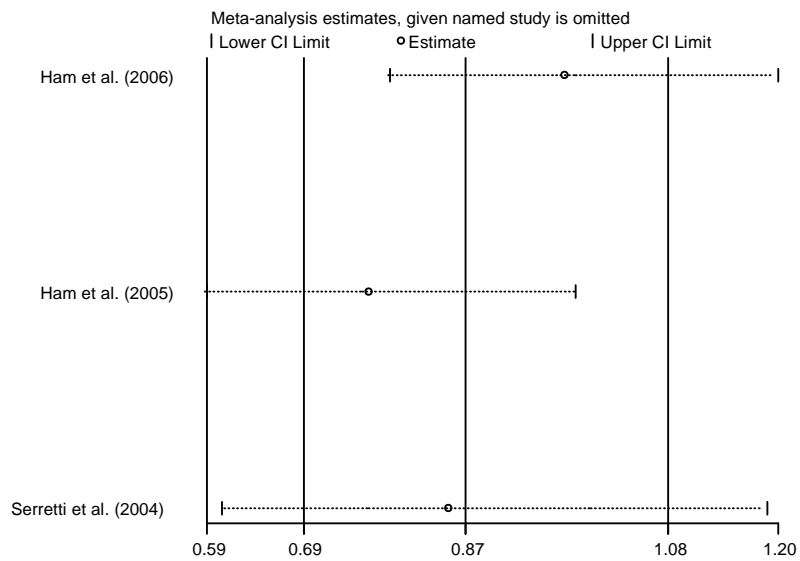
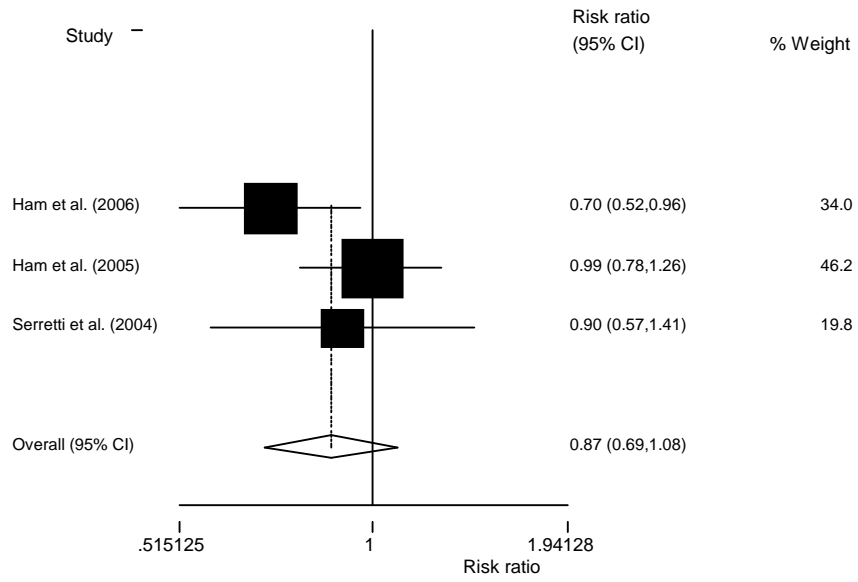


Figure 6. Forest plot from the TPH-1 (A/A vs. C/C) meta analysis and sensitivity analysis plot

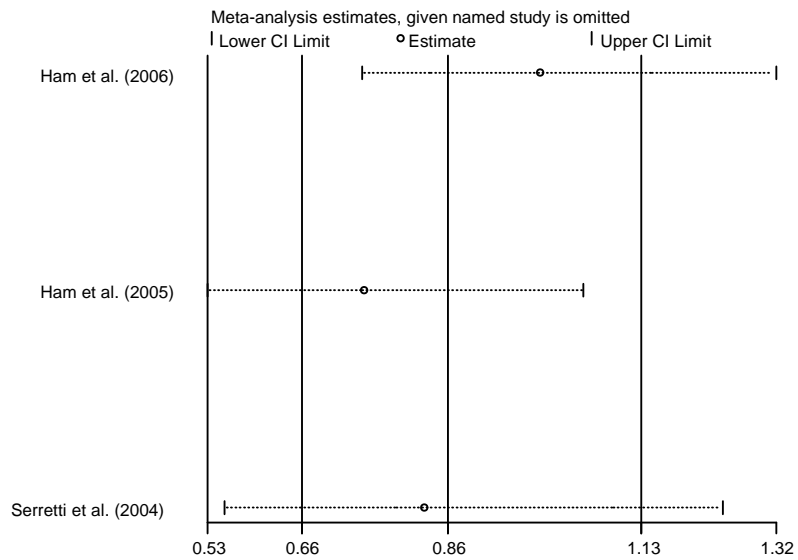
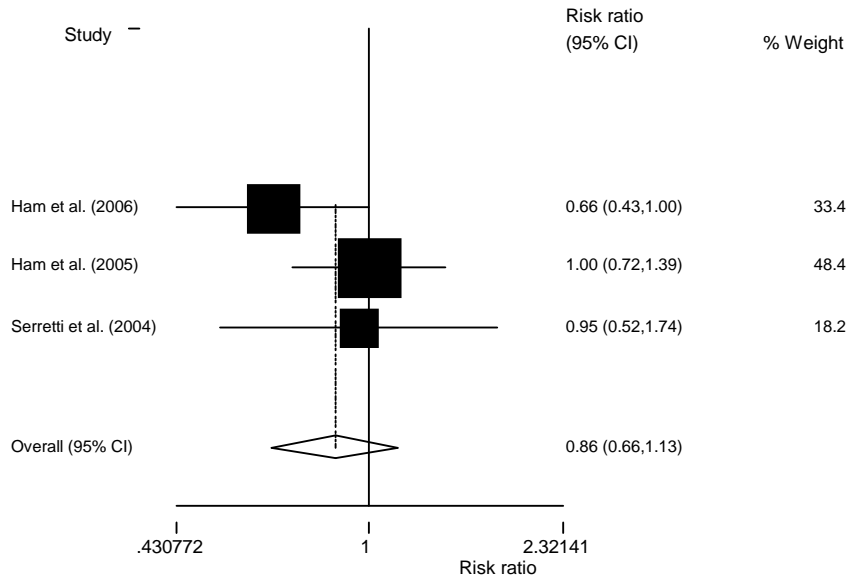


Figure 7. Forest plot from the TPH-1 (A/C vs. C/C) meta analysis and sensitivity analysis plot

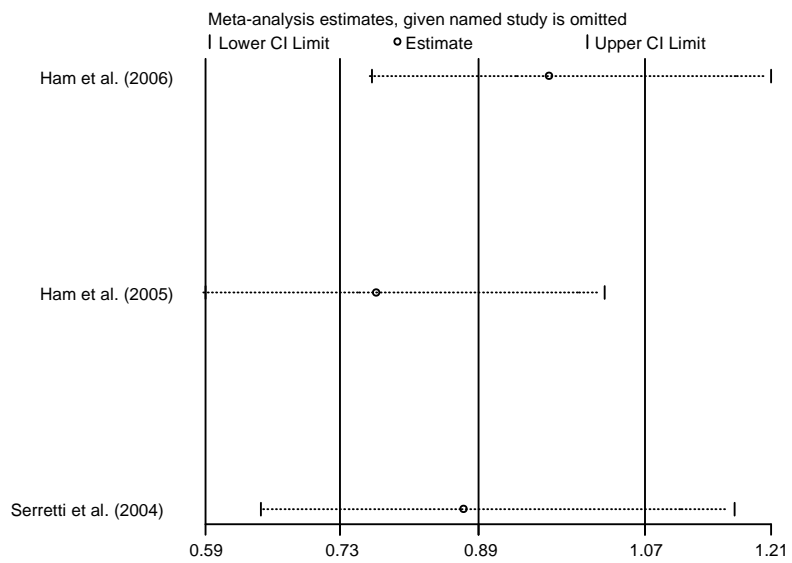
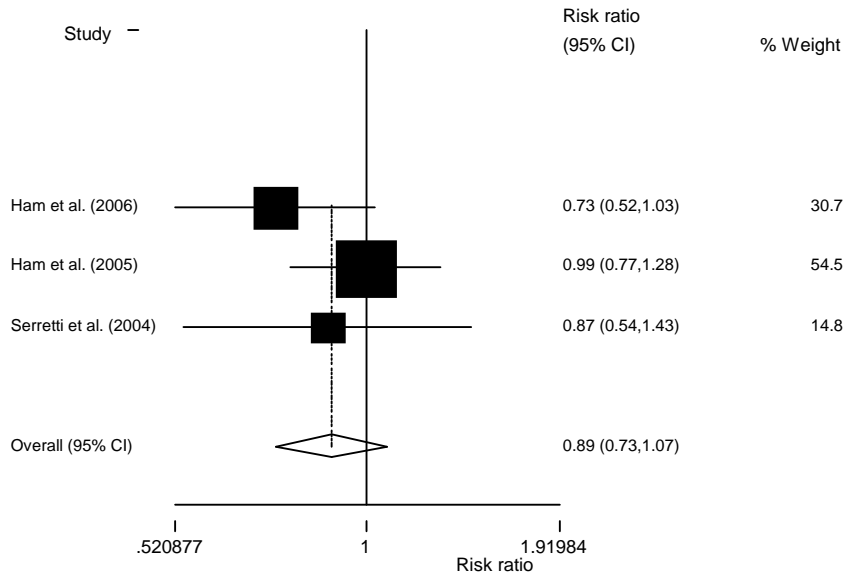
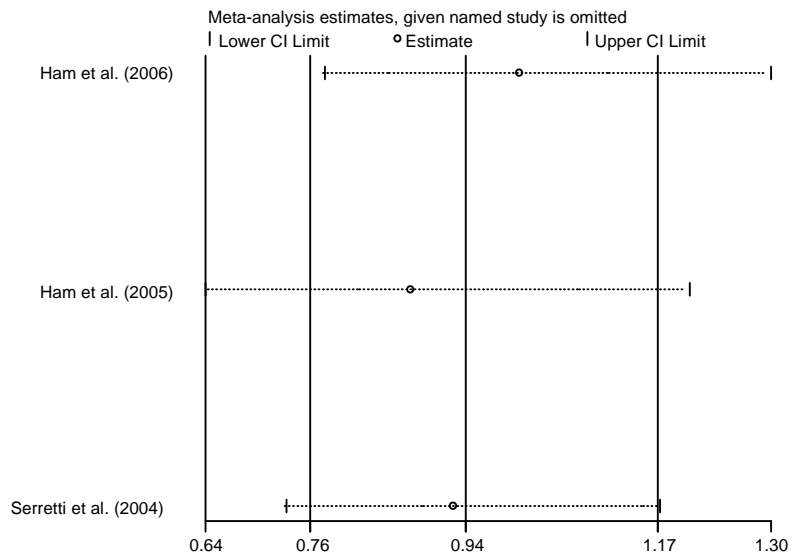
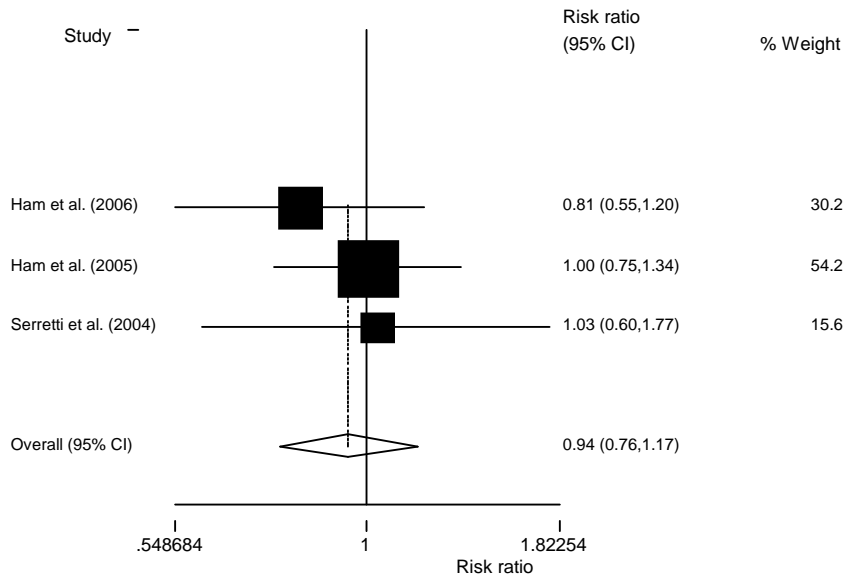


Figure 8. Forest plot from the TPH-1 (A/A vs. A/C and C/C) meta analysis and sensitivity analysis plot



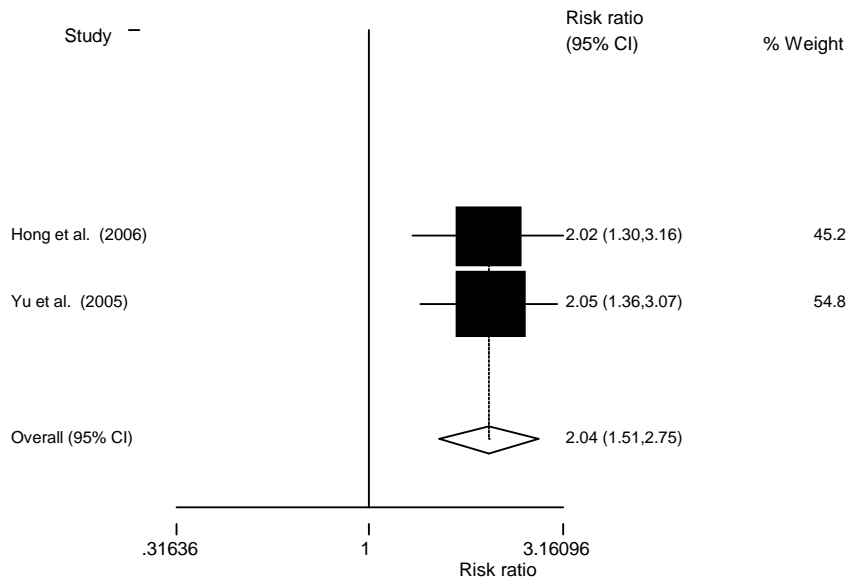
3.4 Meta analysis of the HTR1A gene

The HTR1A gene, expressed as a postsynaptic receptor, has not been previously studied in great detail. Only two studies of the 22 investigated polymorphisms in HTR1A. It has been suggested by <author> that the polymorphism C1019G has an effect on SSRI treatment. It has also been hypothesized that the SSRI antidepressant treatment response is due to linkage disequilibrium between the C1019G polymorph and a nearby functional polymorphism. The meta analysis performed on the two HTR1A studies resulted a p value of 0.09, indicating that the null hypothesis that the response rate ratio is equal to 1 cannot be rejected and that the analysis did not result in statistically significant differences between the genotypes in response to SSRIs. The heterogeneity chi-squared value was 0.00 ($p>0.05$), meaning that the risk ratios are almost the same in both studies and there was very little heterogeneity. The overall response rate ratio comparing C/C to C/G and G/G individuals for the analysis was 2.04 (95% CI: 1.51, 2.75). This statistically significant result infers that patients with the C/C genotype were approximately two times more likely to have a response to SSRI treatment than those with C/G+G/G genotypes. Since there were only two studies, a sensitivity analysis was not performed.

Table 6. Number of responders and nonresponders for HTR1A meta analysis

Study	# responders (C/C)	#		# responders (CG+G/G)	# nonreponders (CG+G/G)
		nonresponders (C/C)			
Hong et al. (2006)	7	3		74	140
Yu et al. (2005)	8	3		75	136

Figure 9. Forest plot from the HTR1A gene meta analysis



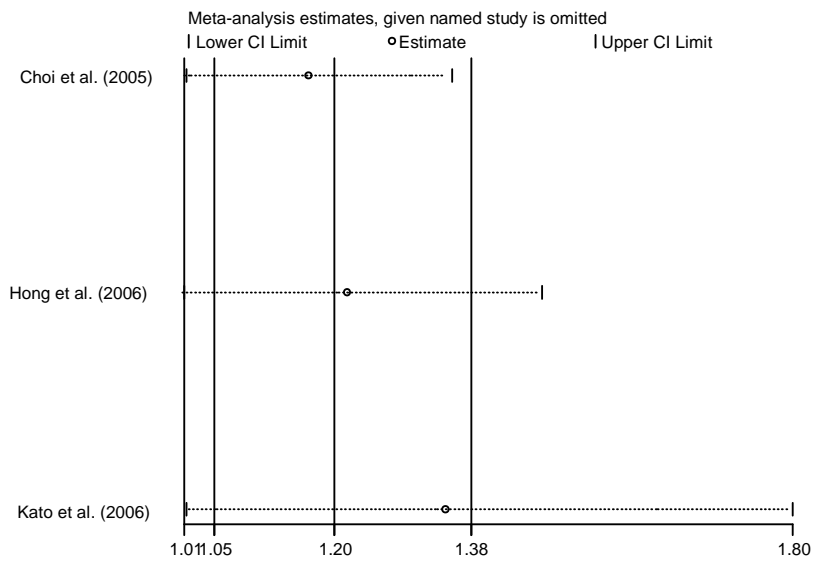
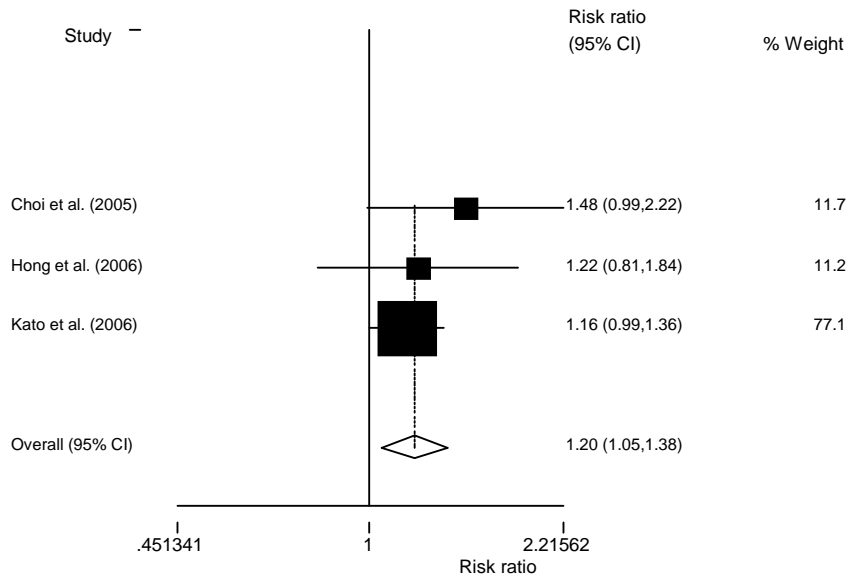
3.5 Meta analysis of the HTR2A

The amount of information on the HTR2A gene and the mechanism of action is limited. The effects that the A1438G polymorphism may have on treatment are even less understood. Only two studies of the 22 collected included the HTR2A gene A1438G polymorphism. The meta-analysis of the two studies yielded a chi-squared value for heterogeneity of 1.22 ($p = 0.544$), which indicates that heterogeneity between the two datasets was low. When the patients with the G/G genotype was compared to the combined G/A & A/A patients, the G/G patients were 20 percent more likely (95% CI: 5% to 38% more likely) to respond to SSRI treatment (response rate ratio = 1.20 (95% CI: 1.05 to 1.38)).

Table 7. Number of responders and nonresponders for HTR2A meta analysis

Study	# responders (G/G)	# nonresponders (G/G)	# responders (A/G+A/A)	# nonresponders (A/G+A/A)
Kato et al. (2006)	19	1	49	11
Choi et al. (2005)	16	7	23	26
Hong et al. (200)	17	23	64	120

Figure 10. Forest plot from the HTR2A gene meta analysis and sensitivity analysis plot



4. Discussion and Conclusion

4.1 Discussion

The data from the past three years have shown that many genes linked to MDD and SSRI treatment are being studied; the main four genes of interest being 5-HTTLPR, TPH-1, HTR1A and HTR2A. Evidence in the literature has demonstrated that each gene has some influence on the efficacy of SSRI treatment for MDD. While mechanisms are still unclear, these clinical studies help understand patterns of genotypes in the population. The meta-analysis of the response rate ratios for each gene demonstrates both the limits of statistical analysis, as well as its usefulness in clinical trials. The lack of available data for pediatric trials with SSRI treatment limits the ability to effectively study the gene polymorphisms at first MDD onset.

The meta-analysis of the 5-HTTLPR revealed statistically significant heterogeneity among the studies, making it difficult to analyze and compare to previous work. This heterogeneity may arise from a number of factors. When considering sources of heterogeneity observed in a meta-analysis, it is necessary to examine characteristics of the study, its data collection methods, and patient characteristics. Potential sources of heterogeneity in the studies included in this meta-analysis are source populations, patient characteristics, country in which the study was performed, sample sizes, treatment allocations (if any), treatments regimens used, types of SSRIs, ascertainment of depression symptoms, and utilization of the HAMD score. These potentially substantial sources of heterogeneity create difficulty in combining the results reliably and generalizing findings to a broader population.

The results from the analysis on the TPH-1 gene suggest that the A218C polymorphism does not affect SSRI treatment. The meta-analysis show that there is no statistically significant difference in relative response to SSRIs between the genotypes A/A, A/C and C/C. Previous

studies have highlighted the possible linkage that A218C may have with A779C. None of the studies that were found for this project looked at this linkage. The treatment response among the different TPH-1 genotypes over all studies suggests that there may be a small effect not seen in these individual studies, or that more research needs to be done.

The HTR1A gene is the least well studied of the 4 genes linked to SSRI response and suicidality from MDD. It is known that HTR1A is a serotonin postsynaptic receptor as well as an auto receptor on serotonergic neurons, but its mechanism is poorly understood. From the two studies done in 2005 and 2006, it has been suggested that the C1019G polymorphism has an effect on SSRI treatment. The results from the meta-analysis agree with the previous studies. The response rate ratios indicate that the C/C genotype is twice as likely to respond to SSRI treatment for MDD. The effects that this particular genotype could possibly have on suicidality, however, are still unclear. More studies need to be done before conclusions can be drawn on its interaction with SSRIs [57].

The last gene that was studied in this paper was the HTR2A gene. Like HTR1A, there is not much known about the interactions it has with SSRIs. Abnormalities in the receptor surface have been found in suicide cases, but no mechanism has been proposed. The studies used in the analysis have shown that the A1438G polymorphism affects the efficacy of SSRI treatment. The current meta-analysis confirms that patients with the G/G genotype are 20 percent more likely to respond than patients with the A/G and A/A genotypes. While the meta-analysis data supports the claim, the fact that there are a limited number of studies devoted to the A1438G polymorphism requires further studies to confirm the previous findings.

In all of the analyses, it was difficult to determine whether each individual SNP modified the effect of SSRIs on a patient's depression symptoms. This difficulty is the result of the various

SSRIs used in the studies analyzed, also the non-uniform treatment methods used when studying a particular polymorphism. In some cases, the limited samples sizes and ethnic groups can affect the generalizability of the data, especially if a specific genotype has a higher frequency in the ethnic group of interest. In order to better understand how certain polymorphisms affect SSRI treatment for MDD, certain clinical criteria may need to be developed to conduct higher quality, standardized studies that could recruit a large, diverse patient population. .

4.2 Future Work

To assess the efficacy of SSRI treatment of MDD in childhood and adolescence, more studies must be conducted. The lack of pediatric clinical data makes it very difficult to determine the effects certain SSRIs may have on suicidality, a major concern in current treatment guidelines for depression. Future pediatric studies need to include large sample sizes of a diverse, generalizable population. Overcoming diagnosis issues is another problem that needs to be addressed. It will be nearly impossible to treat depression if it is not properly diagnosed; sensitive ascertainment of depression symptoms using a more universal score should be developed. Since MDD is a reoccurring illness, treatment a first onset in younger populations is growing concern to the medical community.

One of the goals of future clinical work is to establish studies that address the conceptual gaps in our understanding of the path of suicide among depressed adolescents treated with SSRIs. These studies may be able to properly weigh the benefits with the risks of suicide in adolescent SSRI treatment, a currently controversial issue. Another goal of future research would be to advance the conceptual understanding of pathways to suicide in a high risk, depressed population of first episode MDD. This information could also possibly result in the description of an endophenotype grounded in genetics and maladaptive behaviors that could be used to

identify depressed adolescents at relatively high risk for treatment of emergent adverse events, including suicidality, and thus guide treatment and management of depressed youths.

4.3 Conclusion

Depression is a major health concern in the world today, especially in case of children and adolescents. Diagnosis of MDD at early stages of childhood is critical in effective treatment. Currently, the most effective method of treatment in both adults and youths is drug treatment with SSRIs. Unfortunately, adverse effects can occur while taking SSRIs, including suicidality. Recent studies have shown that some adolescents taking SSRIs are at a higher risk of committing suicide, and have increased the rate of adolescent suicide. This devastating event is an important concern to the patient, doctor, and clinical researchers alike.

Genetic studies have shown that certain genes may play an important role in MDD and its treatment. It has been shown that people with certain genotypes may experience certain adverse effects, including suicidality, while being treated with particular SSRIs. This risk is even greater in adolescents. Four genes have been identified as possible candidates: 5-HTTLPR, HTR1A, HTR2A and TPH-1. Several studies have been conducted to determine the effect these genes may have on suicidality, but the results are not entirely conclusive. Even fewer studies involving these genes have been carried out in pediatric populations.

The meta-analyses performed on the most recent clinical studies involving these genes indicate are not conclusive. The results have shown that most of the data in these trials are too different statistically to be analyzed. The large amount of heterogeneity between studies, along with several other factors, makes it difficult to accurately determine the effects certain genotypes have on SSRI treatment. These results suggest that studies with larger sample sizes, higher quality, and greater generalizability need to be performed to elucidate possible mechanisms for

drug-gene interactions. It also highlights the need for more clinical studies involving adolescents. In order to determine if SSRIs are safe for adolescents, more research needs to be done. The issue of this apparent complex SSRI-gene interaction at hand clearly cannot be easily solved, but further work in the field of pharmacogenetics will continue to have a major impact on drug treatment for depressed children and adolescents.

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