THE ROLE OF NEUROSCIENCE IN INFORMED CONSENT FOR ANTIDEPRESSANTS IN ADOLESCENTS

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Summary

Depression in adolescents shares many features with the disorder in adults, however, it also unique in a number of ways. Like many psychiatric disorders, there is a growing body of evidence that depression is a biologic disorder in both adults and adolescents. Scientific information currently available regarding the genetics and neuroscience of depression in adolescents may be important in establishing a basis for a decision to use antidepressant medication. Due to the complex nature of depressive illnesses, existing studies use scientifically complex designs and the results are not easy to convey to patients or their legal guardians who must make treatment related decisions. This paper reviews selected research on depression in adults and adolescents and summarizes findings in a way that may be helpful in communicating with families considering the use of antidepressant medications. Very strong evidence exists for an inherited susceptibility to depression that interacts with environmental stressors to produce depressive illness in adolescents. Neuroimaging studies demonstrate small regional changes in volumes of specific brain regions in depression and larger functional differences in regional metabolism or neurotransmitter receptor densities. Modern endocrine studies continue to support historically observed abnormalities in reactivity of the hypothalamic-pituitary-adrenal system in depressed individuals. Theories of antidepressant action that involve changes in regulation of monoamines are broadly supported by this literature which also helps to explain the delays in therapeutic response that are typical in antidepressant treatment.

Key words: Depression – Adolescent – Informed Consent – Antidepressant

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Introduction

In adolescent depression, informed consent for antidepressant treatment broadly refers to a process that may begin early in a clinical interaction and includes diagnostic evaluation and patient education. For minor adolescents, this process requires the involvement of their legal guardians, typically their parents. Historically, a higher standard for informed consent has been applied for initiating treatment of minors reflecting a greater level of concern for the safety of minors by both their guardians and by society as a whole.

Standards for informed consent are always specific to individual situations but a number of minimum standards have been described both through court decisions and professional standards. Essential patient specific elements include the ability to communicate a choice, knowledge of the facts, the ability to reason using the facts and the ability to apply this information to the situation (Appelbaum & Roth 1982). Because the consent for treatment of minors is provided by a legal guardian, these factors rarely interfere with the process. When a guardian does not meet these standards, mechanisms for rapidly identifying an alternative guardian through social services exist in most jurisdictions.

The physician's role in obtaining informed consent is far more demanding. Minimum standards have been defined though court decisions regarding malpractice where patients alleged that informed consent was not properly obtained prior to treatment. Historically, the importance of an individual's autonomy has been a factor strongly influencing court decisions in cases related to informed consent and over time, courts have generally increased the demands on physicians to empower their patients in treatment related decisions. An important case defining a standard for informed consent for medical treatment was Natanson v. Kline (1960) in which a patient who experienced necrosis following chemotherapy for breast cancer sued her physician alleging his failure to adequately communicate this risk in obtaining her consent. The court determined that health care providers must provide patients with relevant information to allow them to make an informed

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treatment decision. The nature and extent of what constitutes relevant information was addressed by the US Court of Appeals in Canterbury v. Spence (1972). In this case, a patient, who suffered paralysis following back surgery, alleged that insufficient information about this risk was provided by his surgeon. The court found that a physician must communicate «the inherent and potential hazards of the proposed treatment, the alternatives to that treatment, if any, and the results likely if the patient remains untreated». The court further defined hazards or dangers that must be communicated as «the incidence of injury and the degree of the harm threatened» by a proposed treatment.

The demands on a physician to communicate information to patients was further expanded in the California Supreme Court case of Truman v. Thomas (1982). In this case, it was alleged that a family physician failed to fully communicate the risks of not obtaining a diagnostic test (a pap smear). The patient refused the procedure and subsequently died of cervical cancer. The court found the physician's «duty to disclose is not limited to situations in which the patient consents to the recommended procedure» and «If the recommended test or treatment is itself risky, then the physician should always explain the potential consequences of declining to follow the recommended course of action». Taken together, these legal precedents require physicians to provide a level of information that a «reasonable patient» would use, including risks and benefits of the treatment proposed, of alternative treatments and of no treatment.

Other guidelines regarding standards for informed consent may come from professional organizations or institutional standards. The American Academy of Child and Adolescent Psychiatry issued practice parameters for the treatment of depression which state «before using antidepressants, clinicians should inform parents and patients about side effects, dose, the timing of therapeutic effect, and the danger of overdose» (1998). Additionally, several hospitals or institutions have enacted internal standards for informed consent, frequently requiring some form of signed written consent that must be obtained from a legal guardian. These requirements are designed to help assure that clinicians obtain informed consent properly and that the process is documented. Obtaining a signature from a parent on a hospital consent form may be considered a way of evidencing that informed consent took place but is not a substitute for the legally required process of providing reasonable information regarding the risks and benefits of as well as the alternatives to a proposed treatment.

It is important that the patient understand the disorder that is being treated, first so that they will be motivated to get treatment and second so that they will have a basis for understanding the rationale for a proposed treatment. This is often straightforward when explaining the use of antibiotics for strep throat or surgical treatment of appendicitis. The diagnosis and underlying biologic basis of psychiatric disorders is far more complex, ambiguous and subject to skepticism. Effectively communicating at some level, the biologic nature of a depressive illness provides a basis for the use of antidepressant medications and thus may be required in order to obtain informed consent for this type of treatment. Although current research fails to provide a cohesive understanding of the nature of depression or the action of antidepressant medications, several findings provide clinically relevant insight into both the potential benefits and side effects of treatment. The expected course of treatment as well as the expected course of the untreated illness are also important elements of informed consent that rely heavily on communicating the results of scientific research to patients.

Obtaining informed consent for treatment of a minor may be more difficult than for an adult. A parent or legal guardian may be willing to tolerate risks or side effects of a treatment themselves that they would be unwilling to risk with their child. It is common for a parent or guardian to request a great deal more information regarding proposed treatment of a minor because of their desire to look out for their child's best interests. When an adverse event takes place, often it is considered more serious when it takes place in a child. While informed consent is legally obtained from a guardian, in most cases it is also important to motivate the minor patient to be actively involved in their treatment so that they will cooperate, even if cooperation is simply taking a daily medication. Involving the minor in this way often requires the physician to provide information to and answer questions to the satisfaction of three individuals (both parents and the minor patient).

Recent Food and Drug Administration (FDA) mandated warnings regarding potential increases in suicide risk in adolescents treated with antidepressant medication are another way that the burden on the physician initiating treatment with antidepressant medication has increased over time. The potential severity of this adverse event requires communication of the risk; however, simply listing this risk among other side effects might significantly distort the risk. Informed consent regarding this adverse event requires some description of the complex interaction of the underlying symptoms of depression, the course of illness and recovery, epidemiologic data and recommended monitoring with the adverse event of suicidal behavior. This is another area in which thorough communication regarding the neuroscience of depression and its treatment can provide patients and their guardians with the information necessary to make informed treatment decisions.

Due to the exceedingly complex nature of psychiatric illnesses, neuroscientific research studies generally focus on very narrow aspects of mental illness or treatment in select treatment naïve subjects, often without comorbidities. In order to understand and apply the bulk of this literature, a background in anatomy, physiology, pharmacology and scientific methodology is usually required and is well beyond the background of a typical patient or legal guardian. A physician relating this type of information to patients for the purpose of informed consent must be able to summarize and simplify the information, presenting it at a level appropriate to their patient. An example of this type of simplification familiar to may adolescents was provided in the television and other advertising of the antidepressant Zoloft which reported «people with depression could have an imbalance of serotonin in their brain» and that Zoloft works to correct this imbalance of serotonin levels in the brain» (www.zoloft.com 2006). This description is supplemented in the advertising by animation

of neurotransmitter release and effects on re-uptake. While this should not be considered a basis for an appropriate means of communicating information for the purpose of informed consent, it represents one of the most widely viewed representations of antidepressant action and is an example of an attempt to communicate complex neuroscientific information in a readily comprehensible way.

While legal cases, laws, professional standards, FDA regulations and a variety of other factors shape the informed consent process, they do not provide specifics regarding what information should be communicated in the informed consent for treatment of a depressed adolescent with antidepressant medication. This paper will summarize select neuroscientific research findings that may be relevant to the informed consent for depression in adolescents. Specific sections to be addressed include research on the biologic basis of depression, the mechanism of action of antidepressants, adverse events and the course of treated and untreated depressive illness.

Genetic Studies

Evidence that any disorder is caused by or that an individual is predisposed to based on their DNA strongly supports the possibility that treatment could be provided with medications. Evidence of a genetic linkage in depression has been widely demonstrated through adoption, family and twin studies (Moldin et al. 1991). Communication with a patient or guardian regarding the genetics of depression requires distinguishing the complex multiple gene inheritance pattern suspected in depression from the simpler and more familiar Mendelian patterns that are seen in inheritance of eye color.

A variety of study designs have demonstrated that affective disorders are heritable typically reporting approximately 70% concordance in identical twins with the risk of depression related to both the number of affected relatives and the severity of illness in affected relatives (Faraone et al. 1990). A genetic association between mood disorder and anxiety disorders (Gorwood 2004) has been consistently demonstrated as well as a possible association with psychotic disorders (Tsuang et al. 2004). Both twin and family studies designs have shown that depression and anxiety disorders are distinct but share some genetic risk factors (Middeldorp et al. 2005). In adolescents, genetic factors are important for both depressive and anxiety disorders, however, twin studies have demonstrated that in anxiety, environmental factors play a major role while in depression, one third of the variability is due to genetics with a minimal contribution of environmental factors (Eley 1999).

Genetic factors may play a greater role in depressive disorders that begin in childhood or adolescence because there has simply been less time for environmental factors to have an effect (Camp and Cannon-Albright 2005). A variable that has surfaced in several genetic studies of depression in children and adolescents is a distinction between child or pre-pubertal depression and adolescent depression. Both twin and family study designs support strong genetic factors in the development of depression in both children and adolescents but suggest that pre-pubertal depression may be more influenced by environmental factors than depression first evident in adolescence (Rice et al. 2002). Specifically, pre-pubertal onset depression may be strongly influenced by both genetic factors and environmental stressors such as family discord (Rutter 1997).

While genetic factors have been convincingly linked to the development of depression, a maximum predictive effect of 70% in identical twins suggests that other factors also play a key role in depression. Rutter (1999) suggested that genetic risk for depression is inherited in the form of «sensitivity to environmental stressors» (Rutter et al. 1999). Single gene and even single chromosome theories for the genetics of affective disorders have been inadequate and the genetic influences on affective disorders have been described as most likely due to small effects of multiple genes that confer susceptibility to depression (Johansson et al. 2001). In a recent study of monozygotic twins, genetic influences were the most important factors influencing development of depression but the environmental influence of negative life events was also significant (Liang and Eley 2005). The environmental influence of parenting, while important, was less than the effect of life stressors and much less than the effect of genetics; a finding that may be of interest to parents consenting to treatment of their depressed adolescent and worried that their behavior may be at fault.

More recent genetic evidence supporting genetic factors in the pathogenesis of depression has come from identifying abnormalities in known gene products (such as receptor or transporter molecules) in individuals with depression or studies in animals with mutations in the specific genes that code for these gene products. This type of research, while more precise than family or twin studies, is likely to be more complex due to the multiple factors involved in gene expression and regulation and will be less familiar to patients and their families requiring more explanation to be relevant. Attempts to create animal models of depression using single gene mutations in of a variety of monoamine neurotransmitter systems including serotonin and norepinephrine receptors have failed suggesting that clinical depression probably involves multiple genes (Urani 2005). Approximations of a depressive syndrome have been created in mice with genetically altered expression of corticotropin-releasing hormone demonstrating both depressive and anxiety related behaviors (Deussing and Wurst 2005). Similarly, depression like symptoms have been observed in mice with mutations in genes coding for corticosteroid receptors (Urani and Gass 2003). These studies may point to specific genetic variants associated with depression or simply indicate that factors that disrupt the hypothalamic-pituitary-adrenal system increase risk of depression.

A major focus of research on gene products related to serotonin function has been suicidal behaviors. Several abnormalities have been reported in gene expression of the serotonin system in both suicide attempters and completers; generally these abnormalities suggest reduced function of serotonin or adaptations to reduced function of the system (Mann et al. 2001). A specific polymorphism in the serotonin trans-

porter gene has been associated with suicidal behavior in depression but not with depression itself (Du et al. 2001). Meta analysis has associated a variation in the promotor region of the serotonin transporter gene with suicide attempts (Anguelova et al. 2003). Other authors have concluded that serotonin function is clearly abnormal in suicide but known genetic variations in synthetic enzymes, transporter or receptors have not been consistently replicated or associated with suicidal behavior to date (Arango et al. 2003). In a study that goes beyond gene variations or mutations, Schmauss reported «excessive» RNA editing of serotonin receptors, producing less functional receptors in suicide victims, demonstrating the importance of considering the factors that influence gene expression in genetic research (Schmauss 2003).

Research more broadly into gene products associated with depression has confirmed previous findings; that up to fifty percent of the variability in depression may be due to genetic factors and that gene environment interaction represents the most likely explanation for depressive illness. Similar to findings in suicidal behavior, abnormalities in expression of the serotonin transporter gene have been the most consistent finding in depression (Hamet and Tremblay 2005). Several studies of serotonin receptors and the serotonin transporter have shown some association with depression but these findings have not always been replicated. Consistent findings have included a stronger role for genetics in depressive illness that develops early in life and a role for genetics in depression primarily through the modulation of an individual's sensitivity to stressful life events (Neumeister et al. 2004). In a rare study using a sample of adolescents, Eley et al. (2004) reported that complex vulnerabilities for depression were associated with specific genetic variations in serotonin transport and serotonin metabolic gene products. Gender effects were observed and importantly, the authors concluded that environmental stressors were necessary to see depression.

Recent studies have supported a major role for genetic factors in not only the development of depression but in an individual's response to antidepressant medication (Serretti et al. 2005). Specifically, variations in the serotonin transporter gene have been reported to influence response to SSRI medications (Malhotra et al. 2004). Not only treatment response but also side effects have been reported associated with genetic variations. For example, individuals who exhibit treatment limiting side effects of paroxetine have a higher incidence of a particular genetic variant of the serotonin receptor (Murphy et al. 2003). These findings, although preliminary, suggest that both the development of depression and the course of treatment are strongly influenced by genetic factors.

Endocrine and Immunologic Studies

A role for the endocrine system in depression has been a clear possibility since hypothyroidism or hypercortisolemia were historically linked to depressive symptoms. While these illnesses clearly can cause depressive symptoms, they account for a negligible fraction of the patients presenting for treatment of depression. Reduced reactivity to dexamethasone challenge has been reported in subset of depressed adults but not consistently in children or adolescents. In a longitudinal study design that failed to demonstrate abnormalities in acute depressive illness, adolescents who exhibited elevated serum cortisol near sleep onset did show a significantly increased risk for the subsequent development of a pattern of recurrent depression later in life (Rao et al. 1996). Recent studies have suggested that pre-natal or early life stress leads to elevated cortisol and eventually reduced reactivity of the hypothalamic pituitary adrenal system and ultimately depression (de Kloet et al. 2005). Specifically, corticotropin releasing factor dysfunction has been associated with both depression and anxiety, possibly through a role in the modulation of the activity of monoamines (Keck 2005). Barden (2004) has described a possible etiology for depression involving chronic stress causing release of cortisol that eventually blunts the cortical feedback that is mediated through glucocorticoid receptors. The demonstrated increase in glucocorticoid receptor synthesis in response to several common antidepressant medications could restore normal feedback to the system and be a possible mechanism of action for antidepressant medication. Another possible mechanism for stress to influence the onset of depression is through the immune system. The release of cytokines such as interleukin 1 has been associated with chronic stress and the effects of excessive release of these cytokines in animal models has included depression like symptoms (Simmons and Broderick 2005).

Structural Neuroimaging Studies

One of the most straightforward ways to investigate a neurologic basis of depression is to use neuroimaging to identify structural abnormalities that characterize the disorder. Early studies using radiation based imaging techniques have not demonstrated differences between normal and depressed brains. More recently, the availability of high resolution magnetic resonance imaging (MRI) techniques and sophisticated analytic software have allowed comparisons that could detect differences in brain structures smaller than two cubic centimeters in size. Most studies in adults have focused on the hippocampus or amygdala. Caetano (Caetano et al. 2004), reported finding a smaller volume of the left hippocampus (8%) in depressed adults, and further that the reduction in size correlated with duration of the patient's depressive symptoms. Findings in other structures have yielded results when applied to specific populations; a larger corpus callosum (16 % by volume) was reported in a subset of depressed adults with family history of depression (Lacerda 2005).

MRI studies of depressed adolescents have also reported changes in the amygdala, but some studies have reported larger volumes (left increased by 12%, right by 7%) (MacMillan et al. 2003) and other studies have reported reduced volumes (left side only, 17%)(Rosso et al. 2005). The hippocampus has been reported as 3-17% smaller (MacMaster and Kusumakar 2004, MacMillan et al. 2003) in depressed adolescents or as no different from controls (Rosso et al. 2005). No correlation between the reported changes in volume

with the severity of depression, the age of onset or the duration of illness has been reported in adolescents (Rosso et al. 2005) but the reported changes in amygdala/hippocampal volumes have been correlated with the severity of anxiety (MacMillan et al. 2003). A smaller amygdala has also been reported in adolescents with bipolar disorder (11%) (DelBello et al. 2004). Few studies in adolescents have reported structural changes in other brain regions, however, one study reported a significant increase in pituitary volume (25%) in depressed adolescents (MacMaster and Kusumakar 2004). The studies summarized above have included the approximate percentage change in affected patients compared with controls to illustrate the typically small magnitude of the differences. Equally important is the very large overlap between depressed and control subjects, making it impossible to reliably use MRI findings as part of a diagnostic evaluation.

Functional Neuroimaging Studies

In contrast to structural neuroimaging techniques such as computerized tomography and MRI, functional neuroimaging techniques are used to measure activity of the central nervous system. These measurements can be made in an uncontrolled way but more commonly are made with a subject performing a specific task. Tasks used for the evaluation of depression often involve response to emotional stimuli but cognitive tasks are also used. Functional MRI (fMRI) studies use MRI technology dynamically to show regional brain activity using the different magnetic properties of oxygenated and deoxygenated hemoglobin as an estimate of blood flow and metabolic rate. For example, amygdala activation using fMRI has been associated with recognition of emotional stimuli in adolescents (Davidson and Slagter 2000). FMRI studies have demonstrated differences in brain activity in both depressed adults and depressed adolescents compared with controls. In a design that evaluated predictors of outcome, activation in the amygdala in response to emotional faces was related to clinical improvement in depressed adults 8 months after the task (Canli et al. 2005).

Pre-frontal areas have been strongly associated with selective attention and cognitive performance. Using fMRI, depressed adults were shown to selectively attend to sad stimuli with involvement of medial and orbital pre-frontal regions (Elliott et al. 2002). In a related study, manic adults were shown to selectively attend to happy stimuli with fMRI changes localized in ventral and medial prefrontal areas (Elliott et al. 2004). In a design that controlled for performance on a memory task (due to the generally decreased cognitive performance of depressed patients) Harvey et al. (2005) demonstrated that depressed patients exhibit greater activation of the lateral pre-frontal cortex than controls, suggesting that depressed patients may have to devote greater resources to perform at a given level than controls. Replicating adult findings, Killgore and Yurgelun-Todd (2006) reported increased activity in medial prefrontal areas and anterior cingulate gyrus during a facial emotion recognition task in depressed adolescents.

Another major functional neuroimaging technique is positron emission tomography (PET) which measures metabolism or binding of radioactive particles allowing an estimation of brain activity or receptor density in specific brain regions. Using PET, metabolic abnormalities in depressed adults have been reported in a variety of regions including variable findings in the temporal lobes and increased blood flow to the hippocampus (Videbech et al. 2001). PET has been used to compare cerebral metabolism pre and post treatment. Kennedy et al. (2001) demonstrated increased pre-frontal and reduced cingulate activity following treatment of depression in adults, both effects partially normalizing previously abnormal activity levels. Holthoff et al. (2004) reported decreased metabolism in several regions including left prefrontal, anterior temporal and anterior cingulate cortex and bilateral thalamus, putamen and cerebellum in depressed adults who responded to treatment.

In part because of the established action of antidepressants on serotonin, PET studies of receptor sites in depression have focused on serotonin receptors. In a study of depressed adults serotonin receptor binding potential was approximately twenty two percent lower in frontal, temporal, parietal and occipital cortical regions compared with controls (Yatham et al. 2000). Similar findings were reported in a subsequent study in which reduced binding of serotonin receptors in frontal, occipital, temporal and cingulate cortices was observed in depressed adults (Messa et al. 2003). This study demonstrated reduced binding potential of serotonin receptors in depressed subjects compared with both controls and antidepressant treatment responders, suggesting that successful antidepressant treatment may reverse abnormalities in serotonin receptor binding potential. Age effects were reported in a study of antidepressant treated depressed subjects in which young adults aged 20-30 years, demonstrated a ten percent reduction in serotonin receptor binding potential following treatment while a much smaller effect was observed in older subjects (Meyer et al. 2001). The authors suggested that antidepressant treatment with serotonin reuptake inhibitors may result in a down-regulation of serotonin receptors in younger patients.

Sleep and EEG studies

Reports of significant sleep disturbance are common in adolescent depression. Scientific studies of sleep architecture typically use electroencephalographic (EEG) monitoring throughout the sleep cycle. Some studies have reported shorter rapid eye movement (REM) latency, shorter sleep latency, more REM sleep (Emslie et al. 1994) and greater REM density (McCracken et al. 1997) in depressed adolescents compared with controls. Following up initial negative findings, Emslie et al. (2001) reported that prolonged sleep latency and the presence of suicidal ideation in depressed adolescents predicted future recurrence of depression in adulthood. In a recent study using a large sample size, 51 depressed children and adolescents were compared with 42 controls. No significant differences in sleep were observed; however, depressed subjects' self reports included significantly more sleep abnormalities that were not supported by EEG findings (Bertocci et al. 2005). While strong evidence exists for

sleep abnormalities in depressed adults, the results of sleep studies are inconclusive for adolescents and children Ivanenko et al. 2005).

Course of Antidepressant Treatment

Neuroscience can play a convincing role in establishing a medical basis for depressive illness as well as a rationale for antidepressant treatment. Potentially equally important information to convey during the informed consent for antidepressant treatment is what a patient should expect in treatment. A discussion of treatment should involve more than simply providing a list of side effects associated with a particular medication. Most antidepressants are initiated at a low dose and the dose is adjusted upward gradually to a known effective dose. The absence of a response after a sufficient duration of treatment often suggests a further upward adjustment in the dose of medication. Each of these variables in treatment is driven by research findings. Specific information regarding the probability of both successful and unsuccessful treatment as well as side effects is recommended in a number of precedents and guidelines. Long term data describing the course of depressive illness is drawn almost entirely from retrospective or naturalistic studies due to both the complexity of longitudinal studies and the ethical issues that would prohibit assigning depressed patients to a control or placebo condition on a long term basis. Families may ask reasonable questions regarding the long term outcome for their depressed child or the need for long term treatment, but at this time there are only a handful of studies that partially address this type of question.

Studies have demonstrated both an episodic nature of depression with improvement or recovery from episodes but also that episodes of past depression increase the risk of future episodes (Kessing 2004). In one study that followed subjects with major depression in early adulthood over fifteen years, approximately half had a subsequent episode of depression (Angst and Merikangas 1997). The subset of patients with child or adolescent onset depression who have a positive family history of depression has been reported to have a higher risk for recurrence later in life (Wickramaratne et al. 2000). A ten year follow-up study of depressed adults, showed that depression occurred in episodes which resolved over time but that small residual impairments persist between episodes (Judd et al. 2000). Sub-threshold depressive symptoms also have been demonstrated to improve at long term follow-up but the majority of individuals are still symptomatic if re-evaluated within the first year (Hermens 2004). The presence of these sub-threshold depressive symptoms in late adolescence has been associated with depression and suicidal behavior for the subsequent 7 year period (Fergusson et al. 2005). Reductions in depression are associated with reduced suicide risk, however, if depression persists, suicidal behavior also persists (Ahrens et al. 1995). Specific findings from longitudinal studies of adolescents have included an increase in mean depression scores during puberty in females but that in males the mean does not change as significantly, partly due to improvements in depression in a large subset of males (Laitinen-Krispijn et al. 1999). In a study that related MRI findings to course of illness, MacQueen et al. (2003) showed that a reduction in hippocampal volumes occurs in patients with recurrent depressive illness and that the volume is reduced at the greatest rate early in the depressive illness.

Interpretation of data from studies that examine recovery from depressive illness is complicated by varying operational definitions of recovery and the common finding of residual symptoms. In a study of adults, one year after hospitalization for depression, approximately fifty percent met criteria for recovery and their average time to recovery was 5 months (Keitner et al. 1992). In a follow-up study of depressed adolescents, twenty percent were still depressed one year later and ten percent were still depressed two years later (Keller et. al. 1988). In the year following a depressive diagnosis, adult subjects with dysfunctional families had a lower probability of recovery, a greater level of depression and lower overall level of functioning (Miller et al. 1992). In a study of depressed adolescents, disruption in sleep architecture was associated with a failure to recover from or a recurrence of depression in adolescents (Armitage 2002). Antidepressant treatment studies typically define response in terms of statistically significant improvement in one or more variables in treated subjects compared with subjects receiving placebo. This is considerably different in most cases from a full remission of depressive symptoms and a return to normal functioning but this sort of partial response is a more realistic treatment goal to describe to patients and families.

When discussing the course of depressive illness and particularly the use of antidepressants, it is important to convey to patients and their families what to expect both in describing the probability of successful treatment and the duration of treatment that will be required to see a response. In a recent meta-analysis, Hansen et al. (2005) reported an average of 4-6 weeks to observe clinical response to antidepressant therapy with selective serotonin reuptake inhibitors. In studies of depressed adolescents fifty six percent responded to fluoxetine treatment at 8 weeks (Emslie et al. 1997) and in a subsequent study sixty percent responded to fluoxetine alone and a seventy percent responded to fluoxetine and cognitive behavioral therapy at 12 weeks treatment (March et al. 2004). Better social and cognitive functioning has been associated with response to treatment in depressed adults (Sotsky et al. 1991) while an «early onset of chronic dysphoria» has been associated with a poor response to tricyclic antidepressants (Stewart 2002). Overall, for adolescents, research suggests that only 60-70% of depressed individuals respond to an initial trial of antidepressant medication and the response requires 6-8 weeks (Wong and Licinio 2004). This time course suggests that the effects of medication are indirect, slow effects that may be best explained by gene regulation.

Side Effects and Adverse Events

Questions and concerns from patients about side effects of antidepressant medications are common. The widespread use of serotonin reuptake inhibitors is due

in part to their comparable efficacy to other antidepressants and their low risk of side effects. Precise mechanisms for most side effects (as well as therapeutic effects) are unknown but in contrast to therapeutic effects which often require several weeks, side effects often appear early in treatment. Across comparative studies of serotonin reuptake inhibitors, the efficacy in adults is similar but small differences in side effect profiles have been reported. The most commonly reported side effects are nausea (12-22%), headache (5-21%), insomnia (6-15%), diarrhea (7-15%) and dizziness (7-11%) (Hansen et al. 2005). In a study focusing on sleep effects, serotonin reuptake inhibitors were associated with insomnia in twenty five percent of patients and daytime sedation at high doses; EEG findings demonstrated suppression of REM sleep (Mayers and Baldwin 2005). In a recent multi-site study of more than 400 adolescents using fluoxetine for depression, the most common side effects were not significantly different from the placebo group and were less frequent than reported in studies in adult subjects. Specific side effects reported included gastrointestinal symptoms (10%), headache (10%), insomnia (3%) and sedation (3%) (March et al. 2004). A different group of potential side effects are due to the effects of serotonin reuptake inhibitors on enzyme systems. All serotonin reuptake inhibitors are metabolized by the cytochrome P450 system. Each of the available serotonin reuptake inhibitors also inhibits the activity of these enzymes but there is considerable variability in the extent of inhibition (Sandson et al. 2005). In a patient taking other medications that are metabolized through the cytochrome P450 system, possible enzyme activity inhibition may place a patient at an increased risk for side effects and play a major role in the selection of a specific antidepressant.

The United States FDA requires antidepressant manufacturers to provide warnings to patients regarding suicide risk. Specific language includes a statement that antidepressant treatment has «a greater risk of adverse events representing suicidal thinking or behavior during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%» (FDA 2006). While this warning represents a statistically significant observation from a very large group of pooled studies, suggested reasons for this observed increase in suicidal behavior have been controversial and have included activation of mania or mixed states, agitation, dis-inhibition as well as therapeutic improvement in energy and motivation without a concurrent decrease in suicidal thoughts. In the FDA's analysis, risk of suicidal behavior was negatively correlated with the plasma half life of the antidepressant medications being compared; Weiss and Gorman (2005) suggested that the increase in suicide risk may be due to poor treatment compliance in adolescents and acute discontinuation effects. The accuracy of reports of suicidality themselves have been evaluated and Starling et al. (2004) reported that adolescent self reports of suicidality have remained stable over last two decades but parental reports have indicated increased depression and suicidality possibly reflecting increases only in parental awareness. Overall, the greatest risk for suicide is depression and antidepressants generally lower this risk (Licinio and Wong 2005). Using a meta-analysis of published and unpublished data on use of serotonin reuptake inhibitors in adolescents, Bridge et al. (2005) reported the probability of a positive response to medication is approximately six times the risk of the medication causing an increase in suicidal behavior. A balanced approach to the presentation of this risk of treatment emphasizes the overall risks and benefits of antidepressants with respect to suicidal behavior and includes a rationale for the FDA's recommendation of weekly monitoring of initial therapy as a means to minimize the risks of suicidal behavior associated with antidepressant treatment.

Discussion

Research in the evaluation and treatment of psychiatric disorders in children and adolescents tends to lag behind research on disorders that are common in adults. The results of studies that demonstrate efficacy of treatments of mood disorders in adults have been used to guide treatment in child or adolescent populations and in some cases these studies have been replicated in younger populations. Few, if any treatments are first tested in child and adolescent populations or are designed to address potentially unique aspects of their illnesses. While there is considerably more data on adults, the prevalence of depression in the 15 to 25 year old age group (6.1% 30 day prevalence) is significantly higher than in older age groups with gender effects observable beginning at age 13 when depression is two to three times higher in females than males (Costello et al. 2002). Mood disorders may be qualitatively different in children and adolescents than in adults. Simple evidence for this comes from the consistently lower response rates to medications that are reported in adolescents compared with adults. Another straightforward indication of differences in mood disorders between adult and adolescent populations is the significantly higher rate of attempted suicide in adolescents. In each of these cases, the evidence suggests that rather than being milder or attenuated in some way, depression in adolescents is both more difficult to treat and potentially more severe.

A great deal of attention has recently been paid to the possibility that mood fluctuations and instabilities in children may be early markers for bipolar illness or may even represent a mixed mood state. A thorough review or discussion of these is beyond the scope of this paper; however, this controversy over the diagnosis of bipolar disorder in children highlights the fact that mood stability is related to development and in general improves during the transitions from childhood to adolescence and into adulthood. Developmental effects on mood stability as well as the inclusion of irritable mood criteria for both mania and depression in children and adolescents are potentially important but inadequately researched aspects of depression in this population that may play major roles in the course of illness and treatment.

Recent FDA mandated requirements to provide information to patients regarding the risk of suicidal behavior associated with antidepressant treatment are part of a more general obligation to inform patients

regarding current research related to their medical condition and treatment. The scientific information presented in this article is likely to be out of date within a few years due to advances in understanding of depression. Neuroscience currently provides convincing data supporting a biomedical basis for depression in adults as well as adolescents, however, at this time no scientifically validated cohesive or unifying theory of the etiology of depression exists and in the absence of this information, no specific treatment approaches exist that can prevent or act directly on the causal factors in depression. The absence of a clear etiology of depressive illness means that clinicians should convey both what is known and what is not known about depression and its treatments when obtaining consent for treatment.

One of the things that must be communicated as a part of the informed consent process is a discussion of available treatment alternatives. Antidepressant treatment with serotonin reuptake inhibitors is the most commonly used treatment for depression and has been the focus of this paper. Outcome data suggesting approximately equal efficacy of these medications compared with other antidepressants but generally better side effect profiles is the rationale for their use as first line treatments. A discussion of treatment alternatives that includes other medications such as serotonin-norepinephrine reuptake inhibitors, bupropion and mirtazapine as alternatives to older antidepressant medications is recommended. Beyond a discussion of alternative medications, it is important to describe alternative treatment modalities where available. For adolescent depression, alternative treatments include psychotherapeutic approaches, specifically, cognitive behavioral therapy, both as a primary treatment but perhaps more importantly as an adjunct to antidepressant therapy where it has been demonstrated to significantly improve the response rate (March et al. 2004). While other treatment alternatives exist such as electroconvulsive therapy and transcranial magnetic stimulation, presently there is not sufficient scientific evidence supporting the use of these treatments to include them in a discussion of treatment alternatives for depressed adolescents.

Conclusion

Effective informed consent for depression in adolescents that incorporates current neuroscience does a great deal more than provide the patient and their guardian(s) with the information they need to make a reasonable treatment decision. It will help them to understand their illness and to be motivated to participate in treatment. It will help them understand what reasonable expectations are for treatment as well as the expected time course of treatment. Patients educated in this way can better understand side effects of medication and discriminate minor side effects from those that are dangerous or may limit treatment. Finally, patients who are well informed about their treatment are more likely to be satisfied with their care and less likely to consider legal action in the event of a serious treatment failure or side effect.

Examples of summary findings from neuroscientific research that convey current scientific knowledge include:

- Genetic studies suggest a strong heritable risk for depressive illness, this evidence comes from family and twin studies as well as studies using molecular biology. This heritable risk interacts with environmental factors to result in depression. The genetics are complex involving multiple genes and are associated with other disorders including anxiety disorders.
- Neuroimaging studies have identified structural abnormalities in areas of the brain associated with emotional functions in depressed individuals. Functional neuroimaging has demonstrated abnormalities in cognitive and emotional processing as well as abnormalities in the distribution and capacity of serotonin receptors in depressed individuals. Some studies show a normalization of these abnormalities with treatment.
- Neuroendocrine studies have demonstrated abnormalities in hypothalamic-pituitary-adrenal function in depression that most consistently suggest high levels of stress result in chronic excess of cortisol, interfering with the feedback loops in the system
- Course of illness data suggest both that a significant improvement or recovery from depressive illness is possible and that the presence of depressive symptoms is associated with a higher risk of future depressive symptoms. Treatment studies suggest that response to antidepressant medication requires four to twelve weeks.

Informed consent for antidepressant treatment of adolescents that builds on this type of scientific information, invites patients and their guardians to use scientific data in the same way that a clinician does to make decisions about their treatment and allows them to have all of their questions answered is recommended.

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