Clinical Practice Guidelines for Treatment of Depression in Children and Adoescents

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INTRODUCTION

Prior to 1970s, when the psychodynamic theories provided the primary conceptual model for psychiatric disorders, it was commonly believed that it was developmentally impossible for prepubertal children to experience depression, because of lack of an internalized superego prior to adolescence. It was generally believed that although children exhibited sad affect as a reaction to loss or frustration, they rarely demonstrated sustained symptoms of depression[1,2]. The recognition of 'anaclitic' depression in very young children[3], a condition marked by low energy, low interest, and low mood reflecting unmet basic dependency needs, provided initial challenge to the psychoanalytic theory. Cytryn[4] was the first person to report depressive symptoms (sadness, withdrawal, impairment in functioning, social isolation, helplessness and hopelessness) in young adolescents with chronic medical illnesses. This clinical presentation was first understood as mimicry of adult depression. Later, more and more clinical observations and numerous empirical investigations during the seventies[5-8] refuted the misconceptions that depression doesn't occur in children and adolescents. Researchers provided evidence that typical symptoms of depression could be identified in children and classified in accordance with the adult Diagnostic and Statistical Manual (DSM) taxonomy[9]. This extension of adult classificatory system to children as young as 6 years of age provided clinicians with the necessary tools to identify and treat major depressive disorder (MDD) earlier in life.

Over the last 3 decades, there has been significant amount of research, which has shown that children and adolescents can suffer from depression, similar to that of adults. It is also evident that childhood depression is a chronic and relapsing illness that doesn't remit spontaneously and therefore requires early identification and treatment[5,6,10-12]. Research has also shown that if not treated adequately, childhood depression can have devastating effects. It can lead to increased risk of poor academic performance, impaired social functioning, suicidal behavior, homicidal ideation, and alcohol/ substance abuse[13]. Hence it is very important to recognize and treat childhood and adolescent depression adequately.

The purpose of these guidelines is to present a framework for the evaluation, treatment, and follow-up of children and adolescents, who present with depression. Most of the data presented in these guidelines is from the western countries, as there is only meager research from India and other developing countries. We hope that these guidelines would help in facilitating proper management. However, it is to be remembered that these guidelines are not a substitute for professional knowledge and clinical judgment.

EPIDEMIOLOGY

A number of epidemiological studies have investigated the frequency of depressive disorders in children and adolescents. Prevalence of depression in infant clinic population ranges from 0.5 to 3 %[14-16]. Another recent

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study, in which DSM-IV–based diagnosis was determined from parental response on an age-appropriate and developmentally sensitive semi-structured interview (PAPA) was used, prevalence rate of 1.4% for major depression, 0.7% for depression not otherwise specified, and 0.6% for dysthymia were reported in preschool children. The higher prevalence rates may reflect the greater developmental sensitivity of the PAPA compared with other methods used to assess psychiatric symptoms in preschoolers in earlier studies (Egger & Angold, 2006)[17]. Among adolescents the point prevalence of depressive disorders reported varies from 1.5% to 8% in community and clinical samples, and lifetime prevalence through adolescence is estimated at as high as 20%[18]

Rate of depression also varies with gender and puberty [22-23]. Among depressed children, there is equal gender representation, but in adolescents (post pubertal), the ratio of depression is about two females to one male, similar to the pattern among adults. Studies have also shown that, the onset of puberty is associated with increase in rate of depression and the incidence of depression has a class effect, with higher incidence in children coming from low socioeconomic status[24-26]. Longitudinal studies of children and adolescents with major depression and dysthymia suggest although many of them may have complete recovery and productivity, there is increased risk of recurrent depressive episodes, suicide, and other morbidity[27-31].

DIAGNOSTIC ISSUES

Similar to adults, depressive disorders in children and adolescents are also diagnosed using DSM-IV[32] or ICD-10[33] criteria. In DSM-IV[32] it is suggested that the criteria of "presence of depressed mood" can be replaced by irritable mood in children and adolescents. Similarly, the diagnosis of dysthymia according to DSM-IV criteria requires duration of 1 year in contrast to the two-year duration required for adults. However, some researchers suggested that the DSM criteria generally lack sensitivity to developmental variation in symptom manifestations, and hence it was required to modify the criteria to pick up depression in children. To address this issue, the ''Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood'' (DC; 0-3)[34] was designed specifically to describe and allow for age-adjusted symptom manifestations, but earlier versions were criticized for their lack of specificity and operationalized criteria for disorders proposed[35,36]. However, the most recent DC 0-3-R tried to address this concern, in which diagnostic criteria have been operationalized. But the validity of these revised criteria has not yet been demonstrated. Because of these issues, both diagnostic systems are thought to be insufficient in their current form for clinical use and for facilitating research in preschool psychopathology.

Luby et al[37] suggested that DSM-IV criteria for depression captured only most severely affected preschoolers and missed a substantial number of children with potentially significant, although less severe, symptoms. They suggested that these children could be picked up by modified DSM-IV criteria, in which the strict 2-week duration criteria should be put aside and children with core symptoms of sadness/irritability and anhedonia (even if they did not have the five required symptoms) should be included. They proposed developmentally modified DSM-IV criteria for diagnosis of depression in preschool children. The prominent symptoms of their modified criteria were sad or irritable mood, anhedonia, low energy, eating and sleeping problems, and low self-esteem. Their developmental modification also included a reduction in the duration requirement for persistence of depressed or irritable mood. They suggested that the criteria of depressed or irritable mood (*Depressed mood, as indicated by either the child's direct expression (such as "I'm sad")* or observation by others *(such*

as "the child appears sad or is tearful") and anhedonia must be present for most of the day, more days than not, for at least 2 weeks rather than for 2 weeks persistently. Another modification was that persistent death and suicide themes in play were included in the assessment of suicidal ideation[38]. This modification was proposed based on the fact that preschool children have limited verbal capacity and in whom preoccupation with these themes may manifest via other avenues of expression, including imaginary play. These proposed modifications were also supported by the initial study of emotional development conducted through the EEDP. Further studies are ongoing on preschool depression for testing these modifications which includes a more detailed assessment of the duration of symptoms, which may help in determining if additional modifications are necessary and, if so, what modifications would prove most useful for advancing research in this area.

However, till further evidence becomes available, it may be prudent to diagnose cases using ICD-10 and DSM-IV for diagnosis of depression in children and adolescent. It is also important to remember that subjects who have subsyndromal symptoms, i.e., less than 5 symptoms as per DSM-IV should be diagnosed as having minor depression or depression (NOS)[37].

PHENOMENOLOGY OF DEPRESSION

Although the same DSM-IV criteria of depression which are used for diagnosis of depression in adults are used for children, studies have shown that certain symptoms are more prominent than others at certain ages than others[39]. For example, it is seen that in children younger than seven years, partly because of their limited ability to communicate negative emotions and thoughts with language, manifest depression as general aches and pains, headaches, or stomach aches[40].

Research has also suggested that clinicians should take developmental prospective into consideration. Depression in infants can be secondary to separation from parents and may manifest as apathy, sad facial expression, lack of responsiveness to alternative caregivers, failure to thrive and severe psychomotor retardation[41]. Preschool children although manifest all the DSM-IV depressive symptoms, but anhedonia appears to be more specific symptoms in this age group (Luby et al, 2003)[37]. Preschool children also manifest melancholic symptoms[42]. Further children may show more symptoms of anxiety (including phobia and separation anxiety) and somatic complaints. The sad mood which may be substituted by irritability may manifest as frustration and temper tantrums and behavioural problems.

In the past it was suggested that depression in children often presents as "masked depression", but some of the newer studies provide evidence that children more often manifest typical presentation, and the masked symptoms, most of which was somatization (seen in about 40 % of subjects) occurred less frequently than typical symptoms[37,43]. Adolescent may display more vegetative symptoms in the form of sleep and appetite disturbances along with suicidal ideations and attempts and more impairment than younger children, but less than adults[44].

Further, when children manifest psychotic symptoms as part of depression, it is commonly in the form of auditory hallucinations[45]. Whereas, adolescents usually manifest psychotic symptoms in the form of delusions. It is also important to remember that children and adolescents who manifest psychotic symptoms as part of depression have much higher chance of developing bipolar disorder, compared to adults with similar mani-

festation[46-49]. There is also some evidence to suggest that seasonal affective disorder may occur in youth, mainly after puberty in adolescent who live in regions with distinct seasons[44].

For convenience, some researchers suggest that evaluation of depression in children and adolescent should cover the acronym "DUMPS" [50]. "D" should cover duration of symptoms, depressed mood, defiance & disagreeability and distant or withdrawal behaviour. "U", stands for presence of undeniable drop in educational performance/ grades or interest in school, which is a frequent manifestation in youth. The main reasons are difficulties in concentrating / inability to make decisions and loss of interest and motivation for doing activities that were pleasurable earlier. It is often useful to look at report cards of several years which can help in identifying the beginning of decline of grades, or fluctuations with certain seasons (e.g. a drop every winter). Inability to concentrate and complete the work may be particularly burdensome in high school going youth, where much of academic work/achievement is based on writing, doing laboratory assignments, reading chapters and answering questions etc. Further, a young person who falls behind may start to cut class or become school avoidant leading to compounding of problem. "M" stands for morbid and strange behavior which may be indirect manifestation of suicidal behavior and suicide itself in youth[51]. "P" stands for pessimism, which is a hallmark of depression in children and adolescents[52]. "S" stands for somatic symptoms, particularly abdominal pain and headaches are common in young people[28,53].

COMORBIDITY

Comorbidity in childhood and adolescent depression is a rule rather than exception. It is very important to evaluate for comorbidity as diagnosis of comorbid conditions often influences treatment decisions, and it can also have significant impact on final outcome in terms of recurrence of depressive episodes, suicide attempts, response to treatment and the utilization of mental health services. It is also reported that prevalence and type of comorbid condition varies with age. Among the preschool depressed children, the common comorbid conditions include attention deficit hyperactivity disorder (42%), oppositional defiant disorder (62%) and both attention deficit hyperactivity disorder and oppositional defiant disorder (41%) and only 28 % had comorbid anxiety disorders[37].

It has been reported than about 40–70% of depressed adolescent patients have at least one concomitant condition, and 20–50% patients have two or more comorbid conditions. The most common comorbid conditions in adolescents include anxiety (30–75%), conduct disorder (10–80%), substance abuse (20–30%) and personality disorder (60%)[19,54]. According to the meta-analysis by Angold and Costello[54] anxiety disorders, conduct and oppositional disorders, and attention deficit hyperactivity disorder are 8.2, 6.6, and 5.5 times more common in depressed children and adolescents, respectively. Further, it is suggested that, onset of unipolar depression is known to follow the onset of other disorders, except for substance abuse and panic disorder, which have their onset in adolescence.

Half of children with dysthymia also have comorbid conditions such as anxiety disorder (40%), conduct disorder (30%), ADHD (24%) and enuresis or encopresis (15%); with 15% of patients having two or more of these comorbid conditions[44].

The variable pattern of comorbidity has been said to be a reflection of difficulty in properly identifying anxiety

disorders in preschoolers because of the comparative lack of research clarifying the nosology of this group of disorders and the covert nature of anxiety disorder symptoms[17]. It is possible with future research the ability to characterize and identify internalizing disorders will improve and the patterns of comorbidity of preschool depression may more closely resemble to that occurs in older depressed children[55].

SCREENING

Evaluating a child or an adolescent for depression can be time consuming. Hence, researchers have suggested using various screening methods to evaluate for depression, which includes methods like psychosocial evaluation, use of questionnaires and structured interview. These are discussed in detail by Richardson & Katzenellenbogen[56].

Thorough adolescent psychosocial evaluation: Psychosocial evaluation should cover important areas which can provide glimpses of depression, if present. Many acronyms have been used to describe the key features that should be performed during a psychosocial evaluation. One example is the HEADSS (Home, Education, Activities, Drugs, Sex, and Suicide) evaluation[57]. This type of evaluation allows providers to ask less invasive questions first and to assess day-to-day lives, and not just their depressive symptoms.

Written questionnaire: These questionnaires can be divided into two groups: general mental health screening instruments and depressive symptom scales. The general mental health scales are used to evaluate the presence of behavioral and psychosocial concerns. They often have internalizing disorder subscales but are not specific for depression or other disorders. In contrast, depressive symptom scales are designed to be more specific to the types of symptoms that individuals with depression experience. Two of the brief, self-administered, questionnaire type general mental health screening instruments are: Pediatric Symptom Checklist (PSC) and Child Behavior Checklist (CBCL). The PSC is a one-page questionnaire with 35 questions designed for screening psychosocial problems in youth aged 3 to 16 years. All questions are rated on a 3 point scale (scored 0, 1, or 2), with a total possible score of 70. For children aged 6 to 16 years, a total score of 28 or more is taken as an indication of significant psychosocial impairment. The main version of this instrument is a parent questionnaire, but a child self-report questionnaire is also available for older children. CBCL is one of the most commonly used screening instruments with 113-items that is designed to screen for a variety of behavioral concerns and can be completed by parents. Another version, known as Youth Self-Report Scale (YSR) is a youth-administered (designed for use with adolescents aged 11 to 18 years) version of the CBCL. There are also teacher report forms that can be used to enhance information obtained from parents and youth. In all these scales rating is done on a three-point scale and all the responses are added to calculate a total score based on normative responses for youth of the same age and gender. Total scores above the 98th percentile for internalizing symptoms are considered to be in the clinical range and warrant further evaluation[58]. However, the main limitation of this scale is its length and the complexity of scoring[56].

Depressive Symptom Scales: Many Depressive symptom scales are available to screen individuals for symptoms of depression. The commonly used depressive screening instruments are: the Beck Depression Inventory-II, the Child Depression Inventory (CDI), the Mood and Feelings Questionnaire, and the Patient Health Questionnaire. A brief version of CDI, known as CDI-S is also available, which has 10 questions and requires

just 5 minutes to complete. BDI-II and CDI can also be used to monitor treatment response.

STRUCTURED INTERVIEWS:

The Preschool Age Psychiatric Assessment (PAPA): The PAPA is a structured (interviewer-based) parent interview for diagnosing psychiatric disorders and symptoms in preschool children aged 2 to 5. It covers the period three months prior to the interview (primary period) as well as lifetime occurrence on some symptoms such as traumatic life events[59,60]. It incorporates approaches used by clinicians to gather information on symptoms and experiences from patients while utilizing a standardised process, which improves the consistency and reliability of the information obtained. Definitions of symptoms are present in a glossary. The interviewer questions the parent using mandatory probes until s/he can decide whether the symptoms described by the parent meet these definitions. The entire PAPA takes from 1.5 to 2 hours to administer. The interview is comprised of diagnostic modules that can be administered separately. At the end of each module, there is an evaluation of the disability resulting from the behaviours or emotions. Computerised algorithms generate diagnoses for DSM-IV disorders in addition to the variety of symptoms, impairment, life events and family functioning scores. PAPA has good test-retest reliability for assessing psychiatric disorders, including depression, in young children[61].

Dominic interactive school aged prepubescent children: Due to the cognitive immaturity of school aged children 6- to 11-years-old, Valla et al[62] developed a child self-report approach to the evaluation of most common mental health problems in youth by combining auditory as well as visual symptom items in a computer program, the Dominic Interactive. The problems assessed with the Dominic Interactive include both internalizing (Depressive disorder; Anxiety disorders: Generalised Anxiety; Separation Anxiety; and Specific Phobias) and externalising disorders (Attention Deficit/Hyperactivity Disorder; Oppositional Defiant Disorder; and Conduct Disorder). Akin to a video game, the computer program presents visual and auditory stimuli (cartoon pictures and voice commentary) to provide better information processing and understanding of verbal concepts than either visual or auditory stimuli alone. Due to limited comprehension of abstract concepts in this age group, queries about frequency, duration, or age of onset of symptoms were not included. Consequently, assessments yield only diagnostic approximates. This instrument's psychometric properties have been confirmed in extensive validation studies[63-65].

Kiddie- Schedule of Affective disorders and schizophrenia (Kiddie-SADS): It has multiple versions, which provide a current diagnostic assessment. Some of the versions can also evaluate worst past episode during the preceding year and also provide life time diagnosis[66].

DIFFERENTIAL DIAGNOSIS

As in adults, many psychiatric and medical conditions may mimic depressive disorders in children and adolescents. Broadly the differential diagnosis can be classified as other psychiatric disorders, medical disorders and depression secondary to medications (Table-1).

Table-1: Differential diagnosis of depression in children and adolescents (Adapted from Richardson & Katzenellenbogen[56]).

Psychiatric disorders
Adjustment disorder with depressive features
Anxiety disorders
Attention-deficit/hyperactivity disorder
Specific learning disorders
Substance use disorders (alcohol, heroin)
Eating disorders
Medical disorders
Hypothyroidism/Hyperthyroidism
Anemia
Inflammatory Bowel Disease
Lupus or other collagen vascular disease
Stroke, tumor, or other central nervous system disorder
Infectious etiologies: HIV, hepatitis
Malnutrition
Tumors
Medications
Beta-blockers
Corticosteroids
Neuroleptic medications

Major depression must be distinguished from adjustment disorders, dysthymia, anxiety disorders etc. It is also important to remember that many of these disorders also present as comorbid conditions with major depression. Patients with adjustment disorder with depressive symptoms do not have enough symptoms to meet

criteria for major depression, have functional impairment within 3 months of an identifiable stressor. Further, adjustment disorder is considered as self-limiting with no risk for relapse. However, if the symptoms of adjustment disorder last for more than 6 months, alternate diagnosis must be considered. It is also important to remember that major depression can also follow stressors[44].

Patients with other psychiatric disorders like attention-deficit hyperkinetic disorders, anxiety disorders and specific learning disorder may also exhibit symptoms of low self esteem, demoralization and marked academic problems. Patients with separation anxiety may present with marked irritability and dysphoria, which usually subsides with reunion with parents. Patients with anxiety disorders may also express sadness and irritability along with insomnia, reduced appetite, poor concentration and sometimes suicidal thoughts. Patients with anorexia nervosa also may manifest depressed mood. The major difficulty in distinguishing these disorders from depression arises because of high comorbidity which is seen in childhood and adolescent depression. Taking a good history can at time tease apart these conditions. Usually, patients with attention-deficit hyperkinetic disorders and specific learning disorder have long standing scholastic problem and the depressive symptoms will be secondary to the same. In such patients, addressing school failure problems through medication or altering the school program may also help to diminish depressive symptoms. The marked irritability and dysphoria in patients with separation anxiety usually subsides with reunion with parents. The diagnosis of depression should not be made in patients with anorexia nervosa till the nutritional status is normalized because sometimes the depressed mood may resolve with normalization of nutritional status and body mass. Substance use can also cause symptoms consistent with a depression or substance use can also be triggered by depression. In general, if substance use is responsible for the depressed mood, discontinuing it will result in resolution of the depressive symptoms. Another, important differential diagnosis which must be considered in adolescent girls is premenstrual dysphoria, which is usually self limiting, phase specific and has recurrent course[44].

The depression in children can also be secondary to medical illnesses like hypothyroidism and hyperthyroidism or the physical illnesses can also mimic depression. Hypothyroidism and hyperthyroidism are very unlikely to be present in the absence of other symptoms, such as weight gain, cold intolerance, or constipation. Youth with anemia may present with fatigue but are unlikely to present the full spectrum of depressive symptoms such as anhedonia or suicidal ideation in the absence of comorbid major depression. Similarly, children with malnutrition may have symptoms of weight loss or inability to gain weight along with fatigue, but they lack other core features suggestive of depression. Rheumatologic disorders can be a rare cause of depression in the absence of other inflammatory changes or systemic symptoms. Similarly, children with HIV should have other infections or symptoms associated with HIV and youth with hepatitis usually have some elevation of transaminases. Youth with stroke or central nervous system disorders should have other neurological changes on physical examination. Children with malignant tumors may also present with symptoms of weight loss along with fatigue, but they lack other core depressive features.

Major depression can also occur in the presence of chronic medical disorders like, diabetes and systemic lupus. Identifying depression in the presence of a medical disorder can be difficult when the medical disorder causes sleep disturbance, appetite change, somatic symptoms, and loss of energy. However, feelings of guilt, worthlessness, hopelessness, and thoughts of suicide are unlikely to be due to a medical disorder and strongly

suggest the presence of major depression. Evaluation of depression should also include proper medication history as some of the medications like, beta-blockers and corticosteroids are known to cause subsyndromal depressive symptoms and syndromal depression[56]. If the patient has syndromal depression, diagnosis of depression can be made in presence of medical illness or medications if the depressive symptoms preceded or are not solely due to the medical illness or medications. If this is not possible and the symptoms are severe enough, than diagnosis of secondary depression should be made[56].

COURSE AND OUTCOME

More than 90% of major depressive episodes remit in 1.5 to 2 years after onset, with only 6 to 10% persisting beyond it. In the absence of treatment, the typical duration for an episode of major depressive episode in adolescents is 7 to 9 months[5,49,67-70]. The features which predict protracted course include severity of the index episode, presence of comorbid psychiatric diagnosis including personality disorders, exposure to negative life events, presence of psychiatric illness in parents and poor psychosocial functioning[6,71-73].

Relapse rates in children and adolescents who have been treated for depression range from 34% to 50%.As with adults, the greatest relapse rates in children and adolescents occur during the 6 months to 1 year after withdrawal from acute treatment, regardless of treatment modality[74-76].

Although recovery from major depression is the rule, recurrence is very common. Follow-up studies have reported recurrence rates of 54% to 72% in children and adolescents followed for 3 to 8 years[6, 27, 30, 67,70].

Predictors of increased risk for relapse and recurrence include younger age at onset, increased number of previous episodes, double depression, increased severity of index episode, increased psychosocial stressors, psychotic features in the index episode, ongoing residual symptoms, poor treatment compliance[6,22,2331,76-82],female gender, higher proportion of family members with recurrent major depressive disorder, elevated borderline personality disorder symptoms and conflict with parents (females only)[83]. Whereas, a single episode of major depressive disorder in adolescence, low proportion of family members with recurrent major depressive disorder, low levels of antisocial and borderline personality disorder symptoms, and a positive attributional style (for males only) independently predicts that formerly depressed adolescents would remain free of future psychopathology[83].

There is also evidence to suggest that course of depression varies with age of onset, especially before and after onset of puberty. Children with prepubertal onset of depression are at increased risk for the development of other disorders, like bipolar disorder, in adulthood. In contrast, youth who experience depression in later adolescence are more likely to experience recurrent depression[11, 30, 84].

Bipolar depression is estimated to occur in 20 to 40% of children and adolescent within 5 years of a diagnosis of major depression[85-86]. Factors that increase the risk for development of bipolar disorder in later part of life include earlier onset of depressive symptoms, the presence of psychomotor retardation (confusion, lack of energy), psychotic features of depression, family history of bipolar disorder or psychotic depression, multiple family members with mood disorders, and occurrence of pharmacologically induced hypomania[86].

A mean episode of dysthymia lasts from 3 and 4 years. Dysthymia is associated with an increased risk for psychiatric comorbidity including subsequent major depression, bipolar disorder, and substance use disorders[28,87]. If a patient develops depressive episode, it usually occurs within 2 to 3 years after the onset of dysthymia[28].

TREATMENT OF DEPRESSION

PSYCHOTHERAPIES

Various psychotherapies have been used for the treatment of depression in children and adolescents. Out of the various psychotherapeutic models cognitive behavior therapy (CBT), interpersonal psychotherapy (IPT) and family therapy have been commonly used. Out of these, cognitive behaviour therapy has been used most commonly. Only the data from randomised controlled trials and effectiveness studies regarding these therapies has been reviewed.

COGNITIVE BEHAVIOUR THERAPY

Cognitive Behavior Therapy assumes that depression is caused by or maintained by faulty cognitions or by maladaptive coping behaviors. Therefore, modification of these thoughts or behaviors can lead to resolution of depression. Cognitive Behaviour therapy has been evaluated in a number of controlled clinical trials (6 in children and 9 in adolescents) for treatment of depression.

EFFICACY STUDIES OF CBT IN CHILDREN (TABLE-2):

All the studies done in children are school-based, with self-reported (but not with diagnosed) depression. Although there is considerable variation in the nature of the CBT interventions in these studies, 5 out of the 6 support the efficacy of CBT in reducing depressive symptoms in children. Out of the 6 studies, studies by Stark et al[88,89] and Weisz et al[90] have been reported to meet criteria for at least possible efficacy in terms of design, treatment manuals, appropriate subject selection, measurement, analysis, and results. These studies also include both self-reported and clinician-reported severity indices, follow-up assessments, and rates of recovery to normal levels of depressive symptoms. From the above we can conclude that in children, when CBT is compared to no treatment or to a waiting-list condition there is evidence to suggest that CBT is better in terms of short-term efficacy and probably such an improvement is maintained till 9 months.

EFFICACY OF CBT IN ADOLESCENTS (TABLE-3)

There are 9 controlled studies of CBT for adolescent depression. Seven of the studies have used an experimental design with random assignment; and 2 studies have a quasi-experimental design with nonrandom (alternating) sampling (table-3). Out of these, 7 studies have found CBT to be efficacious at the end of acute treatment. Most include adolescents with diagnosed depressive disorders, and only one was conducted in a school setting. Out of the 9 studies, there are 3 series of studies conducted on CBT for adolescents with diagnosed depression. Each series contains at least one treatment outcome study and additional studies regarding follow-up status, predictors of outcome, or of subsequent course. Some of these studies suggest that CBT is an efficacious treatment for seriously depressed teens and is superior to interventions like family therapy and supportive counseling, whereas, other studies showing the efficacy of CBT similar to placebo. These studies have also shown that certain factors like maternal depression[91-93] may lead to poor response to CBT.

Table-2: Controlled trials of CBT in Children

Author	Comparative group	Sample	Trial duration & sessions	Outcome
Butler et al, 1980[94]	Primarily behavioural Vs Primarily cognitive Vs WL	5th & 6th grade students	Weekly basis for 10 weeks	Primarily behavioral CBT (social skills and problem solving) and primarily cognitive CBT led to better results than the waiting-list (WL) condition, with the primarily behavioral program relatively better.
Kahn et al, 1990[95]	CBT Vs rela•ation therapy only Vs self-modeling only Vs WL	Middle school students	Twice weekly for 6 to 8 weeks	All the 3 active treatments led to significantly better symptom reduction than did the WL. But there were no differences between the active treatments either at the end of treatment or 1 month later.
Stark et al, 1987[88]	Primarily cognitive CBT Vs primarily behavioral CBT Vs waiting-list control	Children of 4th-6th grade (1987) and 4th to 7th grade (1991)	12 sessions over 5 weeks	Both the active treatment groups showed significant reductions in symptoms compared to WL, but neither treatment was superior to the other. More than 75% of the children in the primarily cognitive treatment group and 60 % of children in the primarily behavioral treatment were functioning in the normal range on self-reported depressive symptoms. On clinician interview, all the treated children were in the non depressed range. On follow-up at 5 weeks post-treatment, the treatment gains were maintained in both the active treatment groups, but children in the primarily cognitive treatment were more improved than those in the primarily behavioral treatment.
Stark et al, 1991[89]	Combined group cognitive and behavioral treatment Vs traditional school counseling		24 to 26 sessions over 14 weeks	Both groups improved with less depressive symptoms and cognitions, but children in CBT group showed significantly more improvement.
Weisz et al,1997[90]	CBT Vs no-treatment	Elementary school students	8 sessions	Children treated with CBT had significantly better outcome than no treatment on self-reported and clinician rated depressive symptoms. More children who received CBT (50%) were functioning in the normal range of self-reported depression at the end of treatment than the control group children (16%). At the 9-month follow-up, on clinician ratings, gains were maintained in 69% of children who received CBT in contrast to only 24% of control children.
Liddle & Spence, 1990[96]	Primarily behavioral social competence training Vs attention only Vs no treatment	3-6th grade students	eight, 1-hour group sessions	No difference between the 3 groups at the end of the study

Table-3: Controlled trials of CBT in Adolescents

Author	Comparative group, Sample, Trial duration & sessions	Outcome
Reynolds & Coats[97]	CBT Vs relaxation Vs WL 31 high school students 10, twice weekly group sessions	Both the treatment groups showed significantly greater reduction in self-reported and in clinician-rated depressive symptoms than did the wait-listed control group. There were no significant differences between CBT and rela•ation only. Of the adolescents who had received one of the active treatments, 79% were functioning in the normal range of symptoms by the end of treatment versus none of the waiting-list adolescents. By 5-week follow-up, treated adolescents had ratings in the normal range compared to only 44% for WL.
Lerner & Clum[98]	Problem-solving Vs Supportive therapy, College students with suicidal ideation & self report depression 10 group sessions over 5 to 7 wks	Both treatments reduced suicidal ideation, but CBT was superior in reducing self-reported depression at end of treatment and in reducing depression, hopelessness, and loneliness at 3-month follow-up
Fine et al[99]	CBT focused on social skills training Vs therapeutic support group (TSG) Major depression & dysthymia Group sessions	At the end of treatment, TSG >> CBT on clinician-rated symptoms of depression. 50% of the TSG & 40% of the CBT adolescents were rated in the normal range on clinician ratings, and 50% of the TSG but only 10% of the CBT adolescents were rated in the normal range on self-reported depression. At 9-month follow-up both treated groups were equivalent on all measures.
Rossello & Bernal[100]	CBT Vs IPT Vs WL	Both the treatments were found to be superior to the WL in reducing self-reported depression. Although only IPT had positive impact on self-concept and on social adaptation after acute treatment, by 3 months follow-up, the two treatments were equivalent on these measures as well.
March et al[101]	Fluo•etine Vs CBT Vs Combination Vs pill placebo	CBT not better than pill placebo, whereas fluo•etine alone and combination treatment showed positive effects at immediate posttreatment.
Oregon series studies		
Lewinsohn et al [91], Clarke et al[02]	Adolescent Coping with Depression (CWD-A) Vs CWD-A with parent group (CWD-A1P) Vs WL Diagnoses of major (DSM-IV) or minor depression 14 group sessions of 2-hour each over 7 weeks	Both the treatment groups improved significantly more than the WL controls on self-reported depression, and the CWD-A1P improved more on parent-rated depression. At the end of treatment 43% of CWD-A, 48% of CWD-A1P subjects and 5% of WL subjects achieved remission (defined as no longer meeting diagnostic criteria for a depression diagnosis). At 1 & 6 months follow-up, remission from depression for CWD-A1P was 70% and 82% respectively. Remission was associated with lower initial severity of self-reported depression, lower initial severity of self-reported an•iety, higher frequency and enjoyment of pleasant activities, and less irrational thinking.
Pittsburgh studies		

Brent et al,[93,103] Birmaher et al[71], Kolko et al[104], Brent et al[105]	CBT Vs Systemic behavioral family therapy (SBFT) Vs nondirective supportive therapy (NST) major depression 12 to 16 sessions on weekly basis	At the end of the acute treatment, significantly more number of youth who received CBT (83%) than supportive therapy (58%) no longer met diagnostic criteria for major depression. Remission of depression was also more common in CBT (60%) than in either SBFT (38%) or NST (39%) Symptom relief was faster in CBT than the other two treatments. Pooled data of 3 groups for the predictors of treatment response showed that continued diagnosis of major depression at the end of treatment was predicted by comorbid anxiety disorder, more cognitive distortions, and greater hopelessness at intake. Having entered the study by clinic referral rather than in response to an advertisement also predicted continued depression, a finding mediated in part by greater hopelessness among clinic-referred patients. Lack of history of maternal depression contributed to CBT being much more effective than the other treatments in leading to remission. At 2 years follow-up: no significant difference between groups in terms of remission and recovery rates although the descriptive data again favored CBT (94% in remission) over family (77%) and NST(74%). At the end of acute treatment and at 2-year follow-up, CBT demonstrated specific adaptive effects on adolescents' cognitive distortions and SBFT demonstrated specific adaptive effects on the parent-adolescent relationship. Predictors of response: Comorbid dysthymia and those with more severe self reported depressive symptoms at intake predicted the requirement of additional treatment. During follow up, 48% of CBT, 37% of SBFT, and 40% of NST participants received additional treatments. These adolescents were more likely to have had more severe depressive symptoms at intake, as well as comorbid disruptive behavior disorders and family problems.
British studies		
Vostanis et al[74,106]	CBT Vs Non- focus intervention (NFI) major or minor depression or dysthymia 6 sessions over 14 weeks	At the end of treatment, both the groups improved on diagnostic and psychosocial measures, and CBT = NFI. At 9-month follow-up, both groups continued to maintain gains on self-report measures, but about 25% met criteria for a depressive diagnosis & 45% had significant depressive symptoms during the 9-month period.
Wood et al[75]	Modified CBT Vs relaxation alone major or minor depression 5-8 weekly sessions	Improvement on self-reported depressive symptoms and diagnostic interview symptoms was significantly greater in the CBT group: 54% of CBT group Vs 21% of relaxation group patients achieved remission During the follow-up period, 42% of CBT and 71% of relaxation participants obtained additional treatment. However, at 6 months follow-up there was no difference between the two groups.
Kroll et al[107]	CBT in continuation phase Vs historical controls Sessions: biweekly to monthly basis for 6 months	After 6 months, only one of the CBT-C adolescents had suffered a relapse (cumulative relapse risk of 0.2), compared with six of the control subjects (cumulative relapse risk of 0.5).
Jayson et al[92]	Eight sessions of CBT in the earlier studies	Participants who were younger, had less severe depression, less social and functional impairment and less social stress were more likely to remit.

Effectiveness trials of CBT

Asarnow et al[108] randomized 418 adolescents scoring high on symptoms of depression to either CBT or medication or primary care treatment as usual (TAU) treatment. Treatment was provided over 6 months with average of 3 sessions and at the end of the treatment it was found that subjects in CBT group demonstrated better outcomes over time than TAU and they also preferred to use the services more than the other group. In another effectiveness trial, Clerk et al[109] randomised 152 adolescents with a diagnosis of major depressive disorder to TAU+ SSRI (n=75) or TAU+SSRI + brief CBT (n=77). The CBT program employed cognitive restructuring and/or behavioral activation training. Therapists consulted with prescribing pediatricians to improve medication adherence. At the end of 1 year, a weak CBT effect, with no significant difference between the 2 groups on the primary outcome measure of recovery from depression was noted. However, CBT was found to be better than TAU on the Short Form-12 Mental Component Scale ($p = 0.04$), reductions in TAU outpatient visits ($p = 0.02$), and days' supply of all medications ($p = 0.01$). In another effectiveness trial, Rohde et al[110] randomised 93 adolescents meeting the criteria of major depression and comorbid conduct disorder and assigned them to either CBT or life skills/tutoring control condition. When these patients were assessed post-treatment and at 6- and 12-month follow-up, it was found that subjects in CBT group showed higher recovery from major depression (39%) than the life skills/tutoring control (19%) (Odds ratio 2.66, 95% confidence interval = 1.03–6.85). However, group differences in major depressive disorder recovery rates at 6- and 12-month follow-up were nonsignificant, as were differences in conduct disorder both post-treatment and during follow-up. In another effectiveness trial, Clarke et al[111] randomised depressed adolescent offspring (who met current DSM-IIIR criteria for major depression and/or dysthymia) of depressed parents in a health maintenance organization (HMO) to either HMO care + 16 sessions of CBT (n=41) or HMO care (n = 47). However at 12 and 24 month follow-up the authors were not able to detect any significant advantage of CBT over HMO care, either for depression diagnoses, continuous depression measures, nonaffective measures, or functioning outcomes. In another interesting study, Weersing et al[112] compared the outcomes of 80 adolescents treated with CBT in an outpatient depression specialty clinic (the Services for Teens at Risk Center [STAR]), with a "gold standard" CBT research benchmark and found that the outcomes for STAR adolescents were more similar to the research benchmark when accounting for differences in referral source (clinical versus advertisement) between the datasets.

Meta-analysis of CBT in childhood and adolescent depression

2 metaanalyses have been done of CBT trials in children and adolescents[113,114]. Reinecke et al[113], included 6 studies with 217 subjects in their metanalysis and reported an overall effect size of -1.02 post-treatment, but the overall effect size at follow-up was -0.61. In a recent metanalysis Weisz et al[114] reported an effect size of 0.34, which is significantly inferior to mean ES for other conditions.

Conclusion of CBT

It is difficult to draw strong conclusions from the available literature about CBT on the treatment of depression in children and adolescents. Some studies suggest that CBT is an efficacious treatment for depressed teens and is superior to interventions like family therapy and supportive counseling, whereas, other studies showing the efficacy of CBT similar to placebo. In the metaanalyses also the effect size estimates have fluctuated dramatically. Predictor of response studies and effectiveness studies suggest that CBT may not work well (1) in families with maternal depression[91-93] or parental depression[94], (2) for severe depression and functional impairment[92,93], and (3) in presence of externalizing comorbidity[110,115]. Further, there is evidence to suggest that presence of comorbid anxiety may predict positive outcome of CBT for adolescent depression[93,115]. There is also evidence to suggest that CBT may be more appropriate for cases of mild to moderate depression than severe depression. If patient doesn't respond to CBT alone, combining the same with fluoxetine may be beneficial. There is also data to suggest that CBT needs to be extended beyond acute intervention to prevent relapse after remission; however, the best use of continuation booster sessions remains unclear, as do optimal frequency and duration of such sessions.

Interpersonal Psychotherapy for Depressed Adolescents

IPT was adapted for adolescents' major depression (IPT-A) by Mufson et al[116]. A central theoretical basis of IPT-A is that depression occurs in an interpersonal context and that the onset, response to treatment, and outcomes are influenced by the interpersonal relations between the patient and significant others[117-119]. The IPT-A formulates cases around common adolescent issues including separation from parents, authority concerns with parents, developing dyadic relationships, loss or death of relatives or friends, peer pressure, and problems of single-parent families[116]. IPT has not yet been adapted and tested for patients younger than age 12 years.

IPT-A differs from the adult version in four major modifications: (1) shortening of treatment duration from 16-20 weeks to 12 weeks of individual psychotherapy, (2) adding the involvement of parents, (3) adding a liaison role for the therapist between schools and families, and (4) reconceptualization of the sick role to have a more limited focus (see the later discussion on IPT-A core components). The objectives of treatment take into account adolescents' developmental tasks, such as separation from parents, development of dyadic romantic interpersonal relationships, initial experiences with death/grief, and dealing with peer pressures. IPT-A focuses largely on current interpersonal issues that are likely to be areas of the greatest concern and importance to adolescents[120]. The IPT-A manual has 12 sessions with 50-minute each to be conducted once per week for 12 consecutive weeks[121] with weekly telephone contacts in the 1st month. Patients are educated as to how their depression and the quality of their interpersonal relationships affect one another. The goals of the treatment are to decrease depressive symptoms, educate patients about the link between symptoms and events in relationships, and improve skills for addressing interpersonal problems that may be exacerbating or contributing to the depression. IPT-A is contraindicated in an adolescent with mental retardation, psychotic/bipolar symptoms, substance abuse, eating disorder, obsessive-compulsive disorder and significant expressive or receptive language disorder. Suicidality is not a contraindication for IPT-A. If a suicidal patient has capacity to establish and maintain a therapeutic alliance, depression is less severe, and the patient reports no suicidal plan or intent, then he can be taken up for IPT-A. Before taking the patient for IPT-A, the adolescent has to assure the therapist that he or she will not attempt suicide and will contact the therapist or visit an emergency room in case of a worsening of the ideation. In such patients' therapist monitors the suicidality during the weekly sessions and addresses the use of alternative means of communication or problem solving to express the feelings that drive the suicidal ideation.

IPT-A was tested in the initial open label pilot study by Mufson et al[122]. Fourteen depressed adolescents' females (aged 12–18) were treated with IPT-A and at termination of therapy, there was significant reduction in depressive symptomatology and an improvement in interpersonal functioning. None of the subjects met criteria for any depressive disorder at the conclusion of the study. When 10 of these patients were followed up after 1 year of the initial study, only 1 had relapsed and rest maintained remission from depression. Most of the subjects reported few depressive symptoms and had maintained their improvement in social functioning. There were no reported hospitalizations or suicide attempts since the completion of treatment, and all patients were attending school regularly[97].

Efficacy studies of IPT-A

Individual Interpersonal therapy has been evaluated in only 2 randomised controlled efficacy studies. In a randomised controlled trial Mufson et al[116] reported that at the end of treatment, IPT-A adolescents had significantly fewer symptoms of depression than subjects on clinical monitoring (CM). Further, in contrast to 58% of CM subjects, 88% of patients who received IPT-A, no longer met the diagnostic criteria for major depression and more number of subjects receiving IPT-A (88%) than in CM (46%) completed the trial. Based on the more stringent criteria of low self-reported and low interviewer-rated symptoms, 75% of IPT-A adolescents attained remission from the depressive episode compared to 46% of CM adolescents. Further, adolescents who received IPT-A reported a significantly greater reduction in depressive symptoms, significantly greater improvement in overall social functioning and with friends, and significantly better skills in positive problem-solving orientation and rational problem-solving orientation[116]. In another trial, Rossello and Bernal[100], by using their own modification of IPT with adolescents suffering from major depression, dysthymia, or both compared it with CBT. At the end of the study, although no treatment effects were evident on parent-report measures, but adolescent self report indicated that both IPT and CBT had a significant impact on depressive symptoms. In addition, IPT led to improvements in self-esteem and social adaptation. From these 2

studies it can be concluded that IPT is a useful treatment modality for treatment of depression in adolescents.

Effectiveness study of IPT-A

In an effectiveness study IPT-A was modified to be used at the community level and was compared to treatment as usual in the school based health clinics. Community clinicians were social workers with varied training backgrounds. The clinicians were randomly assigned within each school to receive training in IPT-A. Training included 1 day of didactic lectures and 1 hour of weekly group supervision. At the end of the study, results indicated that IPT-A was better than treatment as usual with a minority, impoverished, high-risk population with mild to moderate depression. The patients who received IPT-A reported significantly greater symptom reduction, significantly higher levels of global and social functioning, and a more rapid improvement in symptoms and functioning (significantly better than the treatment as usual by week 8)[121]. The largest treatment effects occurred in older and more severely depressed adolescents.

Family Psychoeducation

Family psychoeducation have been evaluated as an adjunctive treatment in a randomized controlled trial. Sanford et al[123] randomised adolescents with diagnosis of major depressive disorder criteria to Treatment as usual (TAU) or TAU+ family psychoeducation. Outcome was evaluated at 2 weeks, mid-treatment, posttreatment, and 3-month follow-up. Of the 2 study sites, one site was withdrawn because of poor participant retention. In the second site, no participant missed more than one assessment and there was good family psychoeducation adherence. Compared to controls, participants in the experimental group showed greater improvement in social functioning and adolescent-parent relationships (with medium standardized effect size = 0.5), and parents reported greater satisfaction with treatment.

Antidepressants

About 10 years back there was meager good quality data to show that antidepressants were better than placebo for the treatment of children and adolescents, as most drug trials excluded children and adolescent. Fortunately in the last one decade, some amount of data has accumulated. We will limit ourselves to review of randomised controlled trials, which are considered as a benchmark while evaluating the usefulness of a drug in a particular condition. Surprisingly there appears to be a great deal of publication bias, with negative results not being published. In total 16 randomised controlled trials (Table-4) have been carried out with SSRIs and other newer antidepressants.

Efficacy in short term (Acute phase)

Tricyclic antidepressants: imipramine[124],desimipramine[125,126], nortriptyline[127,128] and amitrip-tyline[129,130] have been evaluated in double blind placebo controlled trials in childhood and adolescent depression. All these studies failed to show any benefit of active drug over the placebo.

Selective Serotonin Reuptake Inhibitors (SSRIs): In terms of efficacy the results of SSRIs have been mixed except for fluoxetine. In all the fluoxetine trials it has been demonstrated that the active treatment group had significant improvement compared to those receiving placebo. The response rates were 50%–60% in the fluoxetine group compared to 30%–40% in the placebo groups. In the most recent, well conducted multicentric community study known as, Treatment of Adolescent depression study (TADS)[101], fluoxetine alone yielded a response rate of 61 % as measured by CGI-I Scores compared to only 35% of those given placebo ($p = 0.001$). Further when fluoxetine was combined with cognitive behavioural therapy the response rate was 71%[101]. Hence, it is not surprising that fluoxetine is the only drug approved by US FDA for the treatment of depression in children and adolescents. In the TADS study, it was also reported that adolescents who were younger, less chronically depressed, had higher functioning, and less hopeless with less suicidal ideation, fewer melancholic features or comorbid diagnoses, and greater expectations for improvement were more likely to benefit acutely than their counterparts. Combined treatment, under no condition was less effective than monotherapy. Combined treatment was more effective than fluoxetine for mild to moderate depression and for depression with high levels of cognitive distortion, but not for severe depression or depression with low levels of cognitive

distortion[131]. The remission data of TADS was presented by Kennard et al[132], who reported that after 12 weeks of treatment, 102 (23%) of 439 youths achieved remission. The remission rate was significantly higher in the combination group (37%) relative to the other treatment groups (fluoxetine- 23%; cognitive behaviour therapy -16%; placebo-17%), with odds ratios of 2.1 for combination group versus fluoxetine, 3.3 for combination group versus cognitive behaviour therapy, and 3.0 for combination group versus placebo. In addition, 71% of subjects across treatment groups no longer met criteria for MDD at the end of acute treatment. Fifty percent of the patients who responded by CGI-I criteria continued to have residual symptoms, in the form of sleep or mood disturbances, fatigue, and poor concentration[132].

The results of other SSRI trials have been mixed. Sertraline was evaluated in 2 identical multicentric placebo controlled trials. Neither of the individual trial showed that sertraline was better than placebo. But when the data of both these trials was pooled the difference between sertraline and placebo reached significance. On the basis of primary outcome, i.e., change from baseline in CDRS-R score; patients receiving sertraline had significantly greater improvement than those given placebo (change in score –22.8 v.–20.2; $p = 0.007$). Further, compared to the placebo group, more patients in the sertraline group were considered responders (69% compared to 59%, $p = 0.05$). Although the trials were not powered to detect differences by age group, there was some suggestion that sertraline may have been more effective among the adolescents than among the children in the study[133]. Although, not reported by Wagner et al[133], in a metanalysis by Whittington et al[134], sertraline had no benefit over placebo on remission. In another recent trial sertraline was compared with cognitive behaviour therapy and a combination of both treatments and it was demonstrated that cognitive behaviour therapy was superior to sertraline, but the combined treatment was not superior to either treatment alone[135].

There have been 3 trials with paroxetine[136-138], but only 1 has been published. In the trial published by Keller et al[136], which also used imipramine besides placebo as a comparator, the primary outcome was measured in terms of reduction in scores on Hamilton Depression Rating Scale (HAMD), and no significant difference was found between paroxetine and placebo group. However, paroxetine was better than placebo in term of secondary outcomes like CGI-I scores and K-SAD-L, but this was also not significant. Imipramine was not found to be significantly better than placebo in any of the outcomes. Two other trials of paroxetine remain unpublished, because they did not show paroxetine to be better than placebo[137,138].

There are 2 placebo-controlled studies of citalopram, one of which was published. In the trial by Wagner et al[139], there was statistically significant improvement in citalopram treated compared to placebo in terms of improvement in CDRS-R scores. This improvement was noted as early as week 1, which persisted till the end of the study. But, despite a positive effect of citalopram demonstrated by the continuous measure, significant difference was not found on CGI between the treatment and placebo groups (47% and 45% respectively had CGI scores that indicated a response). No difference in efficacy was noted in the unpublished study of citalopram.

In the only trial of escitalopram, no difference was found between escitalopram and the placebo group in the primary outcome measure of CGI-I scores. However, among the adolescents who completed the trial, those in the escitalopram group had a significantly greater improvement in CDRS-R scores at the end point than those in the placebo group ($p = 0.047$)[140].

Other Newer antidepressants: In a trial, nefazodone have been shown to better than placebo on some of the outcome measures but not on the primary outcome measure (change in CDRS-R score)[141]. Venlafaxine was not found to be more efficacious than placebo in 3 trials[142]. However when the data of 2 trials was pooled, significant difference was found between venlafaxine and placebo group in adolescents age 12-17 years, but not in children younger than 12 years of age. Two trials of mirtazapine remain unpublished and they did not find any advantage of mirtazapine over placebo (for details, see Cheung et al, 2006)[143].

From the above review we can conclude that there appears to be some evidence of efficacy for paroxetine, sertraline and citalopram, but fluoxetine have been found to be efficacious in more than 1 RCT. However, the evidence is insufficient to support the use of non-SSRIs for the treatment of major depression in children and adolescents.

Table-4: Randomised controlled efficacy studies of antidepressants in children and adolescents

Author	Sample size	Dose	Diagnostics and rating	Age in years	Study duration in weeks	Outcome
Fluoxetine						
March et al[101]	439	Fluoxetine 10-40 mg Vs CBT Vs their combination Vs placebo	K-SADS-PL, DSM-IV	12-17	12	Response to treatment (defined as 'much improved' or 'very much improved' on the Clinical Global Impressions Improvement scale) suggested benefits favouring fluo•etine with CBT and fluo•etine al one over both CBT alone and placebo. Primary analysis of the CDRS-R indicated fluo•etine with CBT produced benefits over fluo•etine alone, CBT alone and placebo. Only a secondary analysis clearly demonstrated an advantage favouring fluo•etine alone over placebo.
Emslie et al[144]	219	Fluo•etine 20 mg Vs placebo	DICA, DSM-IV, CDRS-R	8-18	8	Fluo•etine was associated with greater mean improvement in CDRS-R score than placebo after 1 week ($p < .05$) and throughout the study period. More fluo•etine- (65%) than placebo-treated (53%) patients met the prospectively defined response criterion of ≥30% decrease in CDRS-R score, but this difference was not significant ($p = 0.093$). Significantly more fluo•etine-treated patients (41%) met the prospectively defined criteria for remission than did placebo treated patients (20%) ($p < 0.01$). No significant difference between treatment groups in discontinuations due to adverse events ($p = 0.408$).
Emslie et al[145]	96	Fluo•etine 20 mg Vs placebo	DICA, K-SADS, DSM-IIIR	7-17	8	Using the intent to treat analysis, 27 (56%) of those receiving fluo•etine and 16 (33%) of those receiving placebo were rated "much" or "very much" improved on the CGI scale at end of the study (chi square = 5.1, df = 1, $p = 0.02$). Complete symptom remission (CDRS-R ≤ 28) occurred in only 31% of the fluoxetine-treated patients and 23% of the placebo patients.
Sertraline						
Wagner et al[133]	376	Sertraline 50 -200 mg Vs placebo	K-SADS-PL, DSM-IV	6□17	10	Sertraline had small but statistically significant advantage over placebo Sertraline also produced a small but statistically significant increase in the chance of response (defined a priori as patients who had at least 40% decrease in the adjusted Children' s Depression Rating Scale-Revised (CDRS-R) total score) when compared with placebo. Sertraline had no significant benefit over placebo on remission Adverse events that occurred in at least 5% of sertraline-treated patients and with an incidence of at least twice that in placebo patients included diarrhea, vomiting, anore•ia, and agitation
Melvin et al[135]	73	Sertraline 25-100 mg	MDD, Dysthy-	12-18	12 acute phase,	Following acute treatment, all treatment groups demonstrated statistically significant improvement on outcome measures (depressive diagnosis, Reynolds Adolescent

		Vs CBT Vs their combination Vs placebo	mia, Depressio n (NOS)		6 month open label	Depression Scale, Revised Children's Manifest Anxiety Scale, Suicidal Ideation Questionnaire), and improvement was maintained at follow-up. Compared with antidepressant medication alone, participants receiving cognitive-behavioral therapy alone demonstrated a superior acute treatment response (odds ratio = 6.86; 95% confidence interval 1.12- 41.82). Combined CBT+ antidepressant was not superior to either treatment alone. Although CBT superior to antidepressant medication alone for the acute treatment of mild to moderate depression among youth, this may have stemmed from the relatively low dose of sertraline used.
Citalopram						
Wagner et al[139]	174	Citalopram 20 mg Vs placebo	K-SADS-PL, DSM-IV	7– 17	8	Effect size on the primary outcome measure, CDRS-R was 2.9. At endpoint more citalopram-treated patients (36%) met the prospectively defined criterion for response than did placebo-treated patients (24%), and the difference was statistically significant ($\chi 2$=4.178, df=1, p<0.05). Citalopram also produced a small but nonsignificant increase in the chance of remission (defined as a CDRS-R score of < 28). Citalopram treatment was well tolerated. Rates of discontinuation due to adverse events were comparable to placebo (5.6% citalopram Vs 5.9% in placebo).
MHRA report, 2003[146]	233	Citalopram 10 -40 mg Vs placebo	K-SADS-P	13-18	12	Significant differences were not found on the primary outcome measure (change from baseline on K-SADS-P total score) or any other outcome measures.
Escitalopram						
Wagner et al[140]	264	Escitalopra m 10-20 mg Vs placebo	K-SADS-PL, DSM-IV, CDRS-R	6-17	8	Escitalopram did not significantly improve CDRS-R scores compared to placebo at endpoint (least squares mean difference = -1.7, p =0.31; last observation carried forward). In a post hoc analysis of adolescent (ages 12-17 years) completers, escitalopram significantly improved CDRS-R scores compared with placebo (least squares mean difference = - 4.6, p =.047).
Paro•etine						
Keller et al[136]	275	Paro•etine 20- 40 mg Vs imipramine 200- 300 mg placebo	DSM-IV, HAM-D, K-SADS-L	12-18	8	Paro•etine demonstrated significantly greater improvement compared to placebo in HAM-D total score reduction, HAM-D depressed mood item, K-SADS-L depressed mood item, and CGI score, but it was no statistically significant. The response to imipramine was not significantly different from placebo for any measure. Neither paro•etine nor imipramine differed significantly from placebo on parent or self-rating measures.
Paro•etine (trial no 377)[137]	275	Paro•etine 20 -40 mg Vs placebo	K-SADS-L, DSM-IV,	13-18	12	No differences were found between paro•etine and placebo on the primary outcome variables (> 50% decrease from baseline MADRS and change from baseline in K-SADS-L depression subscale).

			MADRS			At the Week 12 endpoint, 60.5% of paro•etine subjects and 58.2 % of placebo patients had responded (based on 50% decrease in MADRS). Although not statistically significant, older adolescents (>16) tended to show greater improvements with paro•etine than placeb o, while younger subjects (<16) had high placebo response rates. No treatment differences were seen on other outcome variables (CGI Severity, CGI Improvement, BDI, and Mood and Feelings Questionnaire).
Paro•etine (trial no 701)[138]	203	Paro•etine 10 -50 mg Vs placebo	K-SADS-L, DSM-IV	7-17	8	The primary outcome measure (change from baseline on CDRS-R total score) did not show paro•etine to be more efficacious than placebo. Secondary variables (CGI-Severity, CGI-Improvement, and GAF) were also negative. Children (age 7– 11) in the placebo group had greater improvements on the CDRS-R than children on paro•etine (p = 0 .054). No differences were found between paro•etine and placebo in the adolescent group.
Venlafa•ine						
Emslie et al[147]	161	Venlafa•ine Vs placebo	K-SADS-L, DSM-IV	7-17	8	The mean decrease on the CDRS-R was - 18.1 for venlafa•ine & - 16.1 for placebo (p =0.338) Based on CGI-Improvements of 1 or 2, response rates were 50% for the venlafa•ine group and 41% for the placebo group (p = 0.314).
Emslie et al[148]	161	Venlafa•ine Vs placebo	K-SADS-L, DSM-IV	7-17	8	The mean decrease on the CDRS-R was -24.3 for venlafa•ine and -22.6 for placebo (p =0.386) Based on CGI-Improvements of 1 or 2, 68% of the venlafa•ine subjects and 61% of the placebo subjects were considered responders (p = 0.295).
Emslie et al, 2007 (pooled data of above 2 trials)[142]	334	Venlafa•ine 37.5– 225 mg Vs placebo	K-SADS-L, DSM-IV	7-17	8	No difference was found between venlafa•ine and placeb o on the primary outcome (CDRS-R endpoint). In the adolescent group (12– 17), significant differences were found between drug and placebo on the CDRS-R, suggesting that adolescents may show more response to venlafa•ine treatment than younger children.
Nefazodone						
Emslie et al[141]	195	Nefazodone 100 – 400 mg Vs placebo	K-SADS-L, DSM-IV	12-17	8	CDRS-R scores over the entire 8-week trial showed a statistically significant change in favor of the nefazodone (p = 0.03). At week 7, nefazodone demonstrated a significant difference in CDRS-R scores over placebo (- 26.7 vs. - 21.3 respectively, p = 0.006), as well as a 4.0-point improvement in scores by week 8, though just failing to reach significance (-26.5 vs. -22.5 respectively, p =0.055). At week 8 there was a greater increase in CGI response rate (65% vs. 46% respectively, p =0.005), as well as CGI Improvement (2.3 vs. 2.8, respectively, p=0.012), and CGI Severity (-1.7 vs. -1.3 respectively, p =0.022) with nefazodone use. Change in HAM-D scores were also significantly improved in nefazodone group (-

						10.0 vs. - 8.2 respectively, p =0.023), as were scores on CGAS (17.2 vs. 13.0 respectively, p = 0.020).
Mirtazapine						
Mirtazapine (See Cheung et al[143])	126	Mirtazapine 15-45 mg Vs placebo	K-SADS-L, DSM-IV	7-17	8	No significant differences were found on any of the outcome variables. The primary outcome variable, CDRS-R total score at endpoint, was similar for the 2 groups: 35.1 ± 1.6 for Mirtazapine and 37.2 ± 2.2 for placebo (p =0.421). Other depression outcome measures were similar, including mean change in CGI-Severity, and change in HAMD-21 Rates of response (defined as CGI-Improvement of 1 or 2) were also similar between active treatment and placebo (59.8% vs. 56.8%; p =0.75).
Mirtazapine (See Cheung et al[143])	124	Mirtazapine 15-45 mg Vs placebo	K-SADS-L, DSM-IV	7-17	8	None of the outcome measures were significantly different between the two groups. The CDRS-R total scores (primary outcome measure) were 35.4 ± 1.5 for mirtazapine, compared to 38.8 ± 2.1 for placebo (p =0.19). 53.7% of those on mirtazapine and only 41.5% of those on placebo were considered responders based on CGI-Improvement (1 or 2), but the difference was not significant (p =0.2).

SAFETY

Similar to efficacy, safety of antidepressants in children and adolescents is a topic of great interest for consumers, clinicians and researchers. In the controlled trials reviewed, it has been seen that adverse events are common in antidepressant trials with children and adolescents. In most of the trials, adverse events are collected by spontaneous reports from patients and families. Only the multi-site fluoxetine trial used standardized side effects checklist [144] to evaluate adverse events. The most common adverse effects are generally physical, rather than the more controversial and serious adverse events such as hostility, mania or suicide-related events. In addition, although adverse events are common in pediatric trials, adverse events are seen frequently in subjects on both active medication and placebo and only few side effects occur statistically more frequently in the active treatment groups.

Discontinuation due to adverse events: In all of the placebo controlled trials of SSRIs and in some of the SNRIs, rates of discontinuation due to adverse events were reported, which have varied between 2 to 12%. In general, the rates of discontinuation have been higher in the active medication groups compared to the placebo groups with all medications, although the differences where reported were not statistically significant.

Serious adverse events (SAEs): Adverse events are considered to be SAEs if they lead to death, are life threatening (subject was at substantial risk of dying at the time of the adverse event), hospitalization (initial or prolonged), disability (adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life), congenital anomaly/birth defect (there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child), event requires intervention to prevent permanent impairment or damage (a condition that requires medical or surgical intervention to preclude permanent impairment or damage to a subject) and other important medical events (events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience if they may jeopardize the subject or may require medical or surgical intervention, e.g., failed suicide attempts. The various SAEs reported in the active treatment groups are as follows:

- Swollen tonsils in 1 case on fluoxetine[144]
- 11 subjects on paroxetine reported SAEs (1 subject had severe headache requiring hospitalization and the other 10 subjects had various psychiatric events including worsening of depression (2 cases), 'emotional lability' (e.g., suicidal ideation/gestures - 5 cases), hostility or conduct problems (2 cases), and euphoria (1 cases)[136]
- 3 of the paroxetine subjects had agitation and 6 had 'emotional lability'[137]
- 3 subjects on paroxetine had worsening of depression, 1 subject had suicidal ideation (termed 'emotional lability'), and 2 had a suicide attempt (termed 'emotional lability') with subsequent medical conditions (1 hypertension, 1 arm laceration)[138]
- Sertraline: suicide attempt (n=2), suicidal ideation (n=3), aggressive behavior (n=1), hospitalization due to medical problems (n=1)[133]
- Combination of sertraline and cognitive behaviour therapy :1 subject reported suicidality[135]
- Venlafaxine: 1 case of agitation/hostility, 1 case of mania, 2 cases reported worsening of depression, 1 case reported hallucination) and 4 cases manifested suicidal behaviors (4 suicidal ideation and 1 suicide attempt)[142]
- Mirtazapine: 1 case had worsening of depression and suicidal ideation[143]

Behavioral activation, hostility or switch to mania: There were no spontaneous reports of behavioral adverse

events mentioned for fluoxetine[144,145], citalopram, or nefazodone. In contrast, in the TADS study[101], 6 (5%) subjects on fluoxetine (either alone or in combination with CBT) experienced agitation/hostility/irritability versus 4 (4%) subjects on placebo. In the published report of paroxetine, 7 (7.5%) of paroxetine subjects (1 was reported as an SAE) and no placebo subjects reported hostility. In the unpublished study of paroxetine[137], 5 subjects on paroxetine had agitation or hostility out of which 3 discontinued from the study. In the second unpublished study[138], only 1 subject had hostility and was withdrawn from the study. In the sertraline study, agitation was more frequently seen on sertraline than placebo (8.1% vs. 2.3%) among children but no behavioral events were mentioned for adolescents. Venlafaxine study reported 5 (3%) subjects on venlafaxine, compared to 2 (1%) on placebo had hostility as adverse events[147].

Specifically relating to mania, in the citalopram, sertraline and nefazodone trials, none of the subjects developed mania. In total 4 cases developed manic symptoms when the data of the trials was added[144,145] and in the TADS study, mania occurred in 1% of both the fluoxetine alone and placebo groups. However, 3% of subjects on fluoxetine (either alone or in combination with CBT) developed hypomanic symptoms versus 1% of subjects on placebo. In the published study of paroxetine, 2 subjects on paroxetine developed euphoria. Only 2 subjects (1%) developed manic symptoms during the venlafaxine trial[147]. No information is available on mania for the mirtazapine trials[143].

Suicidality: One of the major concerns of prescribing antidepressants in children and adolescents is increase in suicidality. The US FDA conducted an independent examination of the adverse event data from all clinical trials of SSRIs and SNRIs, both for depression and for all indications. Each harm-related adverse event was evaluated and reclassified as "suicidal," "non-suicidal" or "indeterminate." Among the events classified as suicidal were suicide attempts, suicidal ideation and "preparatory actions toward imminent suicidal behaviour." The events classified as non-suicidal included self-injurious behaviours without suicidal intent. They found that when antidepressants were used for any psychiatric condition, the relative risk of suicide-related events was significantly more among subjects given medication for any indication (relative risk - 1.95, 95% confidence interval=1.28–2.98) and major depressive disorder (relative risk - 1.66, 95% confidence interval = 1.02–2.68). The average risk of suicidal events among patients receiving antidepressants was 4%, which was double that seen in patients receiving placebo (2%). This difference was not significant for individual trials, but when the data was pooled this difference was significant. This could be due to the relative rarity of these events (97 among more than 4200 children and adolescents included in the trials). Except for venlafaxine, individual medications were not statistically more likely than other medications to lead to suicidal behaviour.

In the FDA reanalysis it was also seen that there was a large numeric difference between the increased risks for suicide ideation compared with actual suicide attempts for subjects on venlafaxine. Most of the risk-ratio for venlafaxine was driven by suicidal ideation events, rather than by actual suicidal behavior events (all suicide-related events 8.84, 95% CI = 1.12–69.51; suicidal ideation 7.89, 95% CI = .99–62.59; suicidal behaviors 2.77, 95% CI= .11–67.10). This was also true for sertraline. However, in subjects treated with paroxetine, citalopram or fluoxetine, the risk was higher for suicidal behaviors compared to suicidal ideation, although none of these differences were significant between medication and placebo, either by event or for the total.

Based on their reanalysis, US FDA also issued black box warning for antidepressants in children and adolescents. However, data from observational studies involving both adults and youths suggest an inverse relation between treatment with antidepressants and suicidality[148]. During the late 1990s, the incidence of suicide among youths decreased as the number of antidepressant prescriptions increased in the United States, Sweden, Norway, Finland and Denmark[149,150]. A relatively recent epidemiologic study[151] also showed decreased incidence of completed suicides among youths in the United States after adjustment for such factors as physician availability in those prescribed antidepressants. In another similar study from Australia[152], although no decrease in the incidence of suicide was seen despite trends showing increased antidepressant use, but it was found that group which had greatest exposure to antidepressants had a decreased incidence of suicide. Studies of completed suicides also show that the subjects who had been prescribed antidepressants, only less than 10% tested positive for antidepressants at autopsy. Therefore, there is emerging evidence from observational studies

that contradicts the findings of the FDA's review.

EVIDENCE FROM METANALYSIS: EFFICACY AND SAFETY

Four metanalysis have been done which have evaluated the efficacy and safety profile, mainly in relation to suicidality of antidepressants. Although these metanalysis have been conducted over different time periods, each including different number of studies, but the results of these trials are more or less similar, except for metanalysis done by US FDA which concluded that the suicide risk was double in the active treatment group compared to placebo.

Whittington et al[134] carried out a metanalysis of data from randomised controlled trials (published in a peer-reviewed journal and unpublished) that evaluated an SSRI versus placebo in subjects aged 5-18 years. The outcomes which were evaluated included: remission, response to treatment, depressive symptom scores, serious adverse events, suicide-related behaviours, and discontinuation of treatment because of adverse events. They concluded that when the data from two published trials of fluoxetine was analysed there was a favorable risk-benefit profile, which persisted even after adding the unpublished data to the published data. Published results of one trial of paroxetine and two trials of sertraline suggested equivocal or weak positive risk-benefit profiles. However, in both cases, when unpublished data was added, risks outweigh benefits. Data from unpublished trials of citalopram and venlafaxine show unfavourable risk-benefit profiles. They concluded that for all SSRIs (except fluoxetine) and venlafaxine, risks could outweigh benefits of these drugs to treat depression in children and young people.

In the metanalysis conducted by US FDA, which included 24 placebo-controlled trials assessing use of antidepressant medications among more than 4400 children and adolescents, it was concluded that antidepressant medications pose a 2-fold (4% vs. 2%) increased risk for "suicidal behavior or suicidal ideation," although no suicides were reported. This analysis formed the basis of black box warning for antidepressants in children and adolescents[133].

Wallace et al[154] included 10 published and 5 unpublished randomized controlled trials, 22 observational studies, and one crossover trial to assess the cumulative and non-cumulative metaanalyses and generated pooled relative rates of response and serious adverse events. After assessing for inclusion and exclusion criteria only 7 randomized controlled trials for efficacy and 11 randomized controlled trials for safety were included in the metaanalyses. Using cumulative meta-analytic techniques, the efficacy was established and rate ratio for response of SSRI versus placebo remained between 1.2 and 1.3. The single unpublished trial which was included in the metanalysis, even though negative, did not substantially influence interpretation of the overall efficacy rates (by omitting the unpublished trial, relative risk ratio = 1.3; 95% Confidence Interval = 1.2– 1.5). Analysis of safety measure from 11 RCTs revealed that children and adolescents with major depression who were treated with SSRIs were more likely to experience serious adverse events (manic symptoms, harm-related events, including suicide attempt, or other serious event requiring hospitalization and/or study discontinuation) than those who were treated with placebo (relative risk ratio =2.0; 95% Confidence Interval = 1.4–2.8).When the trials were considered individually, 9 of 11 trials showed no statistically significant difference in rate of serious adverse events between SSRI and placebo, and the two trials that suggested SSRIs were associated with statistically greater relative risk of serious adverse events were both published studies[133, 136]. Omission of unpublished trial results did not influence interpretation of safety outcomes. Overall number needed-to-treat to benefit (7.7) verses harm (20.6) suggests relative safety overall; however, confidence intervals for benefit and harm overlapped, suggesting that efficacy over safety was not assured.

In another metanalysis published recently, Bridge et al[155] assessed the efficacy and risk of reported suicidal ideation/suicide attempt of published and unpublished randomized, placebo-controlled, parallel-group trials of selective serotonin reuptake inhibitors, nefazodone, venlafaxine, and mirtazapine in subjects lesser than 19 years, done for pediatric major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and non-OCD anxiety disorders. In total they included 27 trials (15 trials done for major depression, 6 trials for OCD and 6 trials for non-OCD anxiety disorders). Based on data from 13 trials and 2910 participants in major depression, pooled absolute rates of response were 61% (95% CI, 58% to 63%) in subjects treated with antidepressants and

50% (95% CI, 47% to 53%) in those treated with placebo, yielding a pooled risk difference of 11% (95% CI, 7% to 15%), with number needed to treat (NNT) of 10 (95% CI, 7 to 15), and pooled standard deviation of 0.25 (95% CI, 0.16 to 0.34). A similar effect was found in pooled analyses of continuous measures of mean improvement in depression symptomatology (g=0.20; 95% CI, 0.12 to 0.29). Pooled absolute rates of suicidal ideation/suicide attempt were 3% (95% CI, 2% to 4%) in antidepressant- treated participants and 2% (95% CI, 1% to 2%) in those receiving placebo. The pooled risk difference was 1% (95% CI, -0.1% to 2%; P=.08), and the number needed to harm (NNH) was 112.

Authors also reported that although there was increased risk difference of suicidal ideation/suicide attempt across all trials and indications for drug vs. placebo [(0.7%; 95% CI, 0.1% to 1.3%) (Number needed to harm, 143 [95% CI, 77 to 1000)], the pooled risk differences within each indication were not statistically significant: 0.9% (95% CI, -0.1% to 1.9%) for major depression, 0.5% (-1.2% to 2.2%) for OCD, and 0.7% (-0.4% to 1.8%) for non-OCD anxiety disorders. There were no completed suicides. Adolescents appeared to respond better than children to antidepressants in trials of both depression and anxiety. But in children younger than 12 years only fluoxetine and not other antidepressants outperformed placebo in depressed children. Further, in depression trials, efficacy was moderated by age, duration of depression, and number of sites in the treatment trial. The authors concluded that although antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, the effects was strongest in non-OCD anxiety disorders, intermediate in OCD, and modest in MDD. The authors concluded that the benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.

CONTINUATION TREATMENT FOR CHILDHOOD AND ADOLESCENT DEPRESSION

Surprisingly, although many studies suggest that childhood and adolescent onset depressive episodes recur within 5 years of onset[22,23] and the depressive disorder persists into adulthood at a rate of approximately 70%[22,23], only one study have addressed maintenance treatment of depression in children and adolescents[156]. After a 19-week double-blind, multi-site, placebo controlled study of fluoxetine in children and adolescents, the subjects entered into a relapse prevention phase treatment. After a 32-week of relapse prevention phase treatment, the mean time of relapse was longer when fluoxetine treatment was uninterrupted (180.7 days) than when fluoxetine was replaced with placebo (71.2 days) and the difference was statistically significant (p= 0.046). There were similar adverse events between the two groups, and the medication was well tolerated in both. There was no statistically significant association between fluoxetine and events leading to discontinuation in either the fluoxetine-fluoxetine or fluoxetine-placebo groups.

ECT FOR CHILDHOOD AND ADOLESCENT DEPRESSION

Use of ECT in children and adolescents has been marked with controversies since the beginning and till today there is no consensus on use of ECT in this population. Rate of use of ECT in children and adolescents is very low. In 1980, only 1.5 % of the total ECTs administered were given to adolescents in the range of 11- to 20-year. A 1981 mail survey of attitudes toward ECT, conducted in the United Kingdom, revealed that less than 7% of child and adolescent psychiatrists would consider the use of ECT for an adolescent patient[157].

A chart review from Australia revealed that between 1990 and 1995, only 0.93% patients treated with ECT were younger than age 18[158]. Similarly data from other countries also reflects infrequent use of ECT in adolescents and more or less total absence of use in children[159-161].

EVIDENCE BASE

Due to infrequent use there is also relative lack of efficacy data in this population. Most of the data which is available is in the form of isolated case reports, few open label studies, and there are no reported RCTs in this age group. However, in almost all studies done between 1945-1990, in heterogeneous diagnostic groups, except for the study by Guttmacher and Cretella[162], ECT was found to be effective and no serious side effects or fatality were reported with the use of ECT in adolescents. Guttmacher and Cretella[162] reported that ECT was ineffective in three out of the four cases (2 cases of major depression, 1 case each of schizophrenia & Tourette's

disorder). They also noted prolonged seizures (>4 minutes) in 3 of their 4 subjects. On the basis of these observations, they concluded that adolescents respond poorly to ECT and may be more prone to prolonged seizures at energy levels lower than those generally used for adults. The reasons for the exceptionally poor outcome are unclear.

Bertagnoli and Borchardt[163] reviewed the studies published between 1947 and 1990 and concluded that most of these studies had methodological problems, including lack of diagnostic clarity and heterogeneous diagnoses among patients who had received ECT. Early studies also generally relied on retrospective study design and small sample sizes, and they lacked objective outcome criteria. Taking into consideration the methodological limitations of these studies, it is noteworthy that with the exception of study by Guttmacher and Cretella[162], ECT was found effective in all the published reports and no serious side effects or fatality with the use of ECT was reported.

Since 1990, many studies have been published, with 8- 42 adolescents, retrospective in design, with mixed diagnosis. All these studies have shown adolescents benefit from ECT, with best response seen in patients with unipolar or bipolar mood disorders. Schneekloth et al[164], reported a response rate of 65% in 20 adolescents aged 13 to 18 years, 4 of whom had diagnosis of depression. They did not find any correlation between electrode placement and response and any evidence of prolonged seizures in subjects younger than age 15. In a retrospective study, Ghaziuddin et al[165] evaluated the outcome of ECT in 11 children aged 13 to 18 years who had been unresponsive to 3 or more antidepressant trials, 9 of whom had major depression, 1 had bipolar depression and one had organic depression. They reported a response rate of 64%. In another study, Moise and Petrides[166] found a response rate of 76% in 13 adolescents aged 16 to 18 years, 3 of whom had diagnosis of major depression.

In a retrospective study with biggest sample size (n=42), Walter and Rey[158] evaluated the outcome of ECT in subjects aged 14-17 years of age and found a response rate of 51% across diagnoses. Examination of subgroups revealed an 85% response rate among those with psychotic depression[158]. Cohen et al[167] reported a response rate of 100 % for patients with depression, in a retrospective study of adolescents aged 14 to 19 years. Strober et al[168] studied 10 adolescents, aged 13 to 17 years, who received ECT between 1978 and 1996, 7 of whom had major depression and 3 had bipolar depression. They found that with ECT, 60 % of patients achieved full remission and 40 % of patients had partial remission which was maintained at 1-month follow-up.

Bloch et al[169] compared the experience with ECT in adolescents and adults. They found that ECT was equally effective for adolescents and adults (58% in each group achieved remission). The main difference was the diagnosis for which patients were referred: most of the adolescents were in the "psychotic spectrum", whereas most of the adults were in the "affective spectrum". In a similar study, Stein et al[159] retrospectively analyzed the files of all 36 adolescent (between the ages of 13 and 19) and 57 randomly selected adult inpatients (above the age of 20) treated with ECT. They found that 61% of the adolescents and 83% of adults improved by the end of treatment, and 53% and 49 % of adolescents and adults respectively were not hospitalized in the subsequent year. In contrast to the findings of Bloch et al[169], most adults in the study of Stein et al[159] were treated with ECT because of schizophrenic disorders and almost half of the adolescents received ECT for affective disorders. Significantly more adolescents were treated with ECT because of acute life-endangering conditions (catatonia or severe suicidal risk). No significant adverse effects were found in both groups. No differences were found in treatment procedure, with the exception of more adolescents receiving bilateral ECT. None of the patients in the adolescent group complained of a significant subjective memory disturbance, compared with 16% of the adults. ECT was discontinued in 19% of the adolescents because of adverse effects (e.g., manic switch, prolonged seizures, and severe headache), whereas only 1 adult patient had to stop ECT because of an adverse effect (severe headache).

In a review Rey and Walter[170] reviewed 60 studies involving 396 patients younger than 18 years of age (only 5 of these were younger than 12 years) and reported 63% remission rate for the patients with depression. Three quarters of patients with catatonic conditions, regardless of the underlying psychiatric morbidity, showed a significant improvement with ECT. They also concluded that ECT was administered almost always after other treatments have failed and when a patient's symptoms are incapacitating or life threatening and a considerable

improvement with ECT was seen in approximately 90% of adolescents with depression who were resistant to pharmacotherapy. In 2 other reviews done by Ghazuiddin et al (2004)[171] and Stein et al (2006)[172] which included other available studies and case reports the efficacy of ECT in depression ranged from 60% to 100%.

From the above it can be concluded that overall rate of response to ECT among adolescents varies between 50% and 100% and as in adults, ECT is an effective treatment in adolescents.

Adverse effects

Fatality: No fatalities have been reported in all 60 published reports of ECT reviewed by Rey and Walter[170]. In a case series, a 16-year-old girl with neuroleptic malignant syndrome and a stuporous state who received 8 ECTs without improvement died of cardiac failure after 10 days of last treatment. Most likely cause of death was continued administration of neuroleptic medication despite her neuroleptic malignant syndrome[172].

Premature termination of treatment: Only 5 of 396 ECT treated children and adolescents described in Rey and Walter's review[170] ended their treatment prematurely because of adverse effects, including manic switch[166], agitation[174], marked confusion[175], and Neuroleptic malignant syndrome associated with droperidol administration before and after ECT[160]. In the recent review by Stein et al[159], ECT was discontinued in 19% of the adolescents because of manic switch, prolonged seizures, or severe headache.

Prolonged seizures: Prolonged convulsions, defined as convulsions that last for more than 180 seconds[176], have been described infrequently (approximately 20 young patients among more than 600 patients treated with ECT).

Cognitive functioning: Only few publications have addressed directly the long lasting cognitive effects of ECT in adolescents. Cohen et al[176] in a follow-up study of adolescents who were treated with ECT after 3.5±1.7 years reported that 6 out of 10 patients complained of memory loss at the immediate post-ECT period and only 1 patient reported subjective memory loss at follow-up. This group of adolescents was compared with controls matched for gender, age, and diagnosis. Standardized neuropsychological batteries did not reveal significant group differences on tests of short-term memory, attention, new learning, and objective memory scores. Poorer cognitive performance was significantly associated with greater psychopathology. In a subsequent study of these patients, Taieb et al[177] reported that at a mean of 5.2 years after treatment, no difference was shown between the research and control groups in school achievement. Impact on school achievement also was related to the severity of mood disorder rather than to the use of ECT.

Ghaziuddin et al[178] retrospectively assessed the extent of cognitive deficits and recovery of cognitive functions among 16 adolescents treated with ECT. The authors compared the findings of cognitive tests completed before ECT, 7.0 ± 10.3 days after the last treatment, and 8.5 ± 4.9 months after last ECT treatment. Significant impairment in concentration, attention, verbal and visual delayed recall, and verbal fluency was reported in the first post-ECT testing. Complete recovery with return to pre-ECT functioning was noted at the second post-ECT testing. There were no deficits of motor strength, executive processing, and problem-solving capacities during the initial or subsequent assessments. These studies provide preliminary evidence that the cognitive functioning of adolescents treated with ECT is similar to that of controls and that it is likely to return to baseline level several months after ECT. Because of the paucity of systematic well-designed prospective large-scale studies, however, definite conclusions regarding the lack of post-ECT memory disturbances cannot be reached.

INDIAN RESEARCH:

Depression in children and adolescents has been addressed by only few studies from India. There are no studies on evaluation of antidepressant efficacy in Indian population.

Prevalence: Sreenath, et al[179] from Bangalore evaluated the prevalence of psychiatric disorders in children aged 0-16 in the community sample and reported that depressive episodes occurred in 0.1% of children in the 4-16 year age group and no child in the age group 0-3 was diagnosed to have depression. Among the population screened: urban middle class, urban slums and rural population, depression was found only in urban middle

class population. In a clinic based study, Malhotra et al[180], analysed the data of all the subjects attending the child guidance clinic at PGIMER, Chandigarh for the period of 1984-1988 and reported a clinic prevalence rate was 1.2%. In another study, from the same centre, in which clinic data of 1991-1996 was analysed, Malhotra et al[181] reported that out of the total clinic population 2% of cases were diagnosed as having affective disorders, majority of whom (more than two–third) had diagnosis of unipolar depression. In clinic based studies from New Delhi, Sidana et al[182] reported a clinic prevalence of 6% in children aged 2-12 years and Chadda et al[183] reported a clinic prevalence of 3%. In clinic based studies from Bangalore, Srinath & Bavle[184] reported a clinic prevalence of 9.2% and Choudhury et al[185] reported a prevalence of 6 % of for affective disorders. When these children were followed up upto October 1993, eight patients continued to have the diagnosis of unipolar depression and 3 had diagnosis of MDP (circular) depression.

Clinical Profile: Clinical profile of depression has been studied in few clinic based studies. Patel et al[186] studied the symptomatology of depression in adolescent girls of class 10th to 12th from four high schools of Baroda on abridged version of Beck Depression Inventory and life events check list. Of 740 valid responses, 140 (18.9%) girls scored 9 or more on BDI, suggesting moderate/severe depression. The authors also noted that depression was associated with more frequent perception of fair or poor health and lower academic performance. The life events commonly reported by the depressed girls included death of a family member, change in residence, failure in examination, end of a relationship and serious illness.

In a retrospective study, Krishnakumar and Geeta[187] evaluated the risk factors, clinical features and co-morbid disorders of depressive disorder in children below the age of 12 years. Over the period of 4 years (January 2000 - December 2003) 26 boys and 19 girls met the DSM IV diagnostic criteria for Major Depressive Disorder, Single episode. The risk factors identified for depression in the study included stress at school and family, family history of mental illness. The clinical features included diminished interest in play and activities, excessive tiredness, low self- esteem, problems with concentration, multiple somatic complaints, behavior symptoms like anger and aggression, recent deterioration in school performance and suicidal behavior. Tharoor et al (2002)[188], in a retrospective study, described the socio-demographic profile and symptomatology of 102 children and adolescents who were clinically diagnosed as having depression. There were 43 females (42.2%) and 59 (57.8%) males in the total sample, with mean age of 11.9 ±2.2 years for females and 11.6± 2.38 years for males. Most common comorbidity was anxiety disorders (14.7%), which was followed by dissociative disorders (9.8%) and adjustment disorder (5.8%). Family history of psychiatric illness was present in 29 females (67.8%) and 31 males (52.5%). Most common presenting complaints of the children were multiple somatic complaints (40.1%), followed by low mood (38.2%), decreased interest in school (32.3%), death wish (17.6%). In 6% of cases, history revealed prolonged absence or death of a parent and 28% had a precipitating event before the onset of the episode. In another study, Bhargava & Sethi[189] compared the presentation and symptomatology of childhood and adult depression. Thirty two children diagnosed as having major depressive disorder as per DSM-IV criteria were compared with 20 adult patients diagnosed with major depressive disorder as per DSM-IV criteria. The pediatric depression group included more of male children from urban nuclear families. The adult group also had male preponderance. There was statistically significant difference between the two groups on the variables of family type and the family size. More children belonged to the nuclear and small families as compared to the adults. However there was no difference between the 2 groups in terms of family history of the affective disorder, type of onset and presence of precipitating factors. The comorbid conditions in the children included attention deficit hyperactivity disorder, anxiety disorder and the dissociative disorder; whereas in the adult group the co-morbid conditions were substance abuse and anxiety disorder. However, in terms of symptomatology, more children than the adults presented with the somatic symptoms and the predominant mood symptom/s in the children was irritability in contrast to sadness in adults. In term of dysfunction, children presented exclusively with poor scholastic performance and reduced play activity where as the adults presented with the poor work performance. In another study from NIMHANS Bangalore, Bhargava Raman et al[190] reported that many a time's subjects with BPAD-II are diagnosed as having only major depression and past history of hypomania is missed. In their study of 61 subjects diagnosed as having major depression, 20% of subjects had diagnosis of hypomania in the past.

Comorbidity: In the study of Krishnakumar and Geeta[187], majority of children were reported to have comorbid disorders in the form of dysthymia, anxiety disorders, conduct disorder and conversion disorder. Tharoor et al[188]

reported anxiety disorders (14.7%) being the most common comorbid conditions, which were followed by dissociative disorders (9.8%) and adjustment disorder (5.8%). In the comparative study of children and adolescents, Bhargava & Sethi[189] reported attention deficit hyperactivity disorder, anxiety disorder and the dissociative disorder as the common comorbid conditions in children, whereas in the adult group the co-morbid conditions were substance abuse and anxiety disorder. In a study consisting largely of adolescents presenting with school refusal, major depression was present in more than 60% of cases[191].

Outcome: short term outcome studies from India have indicated a remission rate of 84% in clinic based studies with average duration ranging from 7-24 weeks[192].

From the above, it can be concluded that available Indian literature doesn't compel for any particular considerations to be taken into account while developing the clinical practice guidelines.

RECOMMENDATIONS FOR CLINICAL PRACTICE

The treatment recommendations that follow are for depressed children and adolescents. As discussed above, most of the literature is available in relation to depression in adolescents. For children of preschool age and early school years these guidelines will serve as only a broad framework and the clinician should use their experience and emerging literature while planning treatment. The first step of treatment plan comprises of a through assessment. As in adults, the treatment consists of three phases: acute phase, continuation phase and maintenance phase. For writing the recommendations for clinical practice following guidelines were reviewed:

1. Texas Children's Medication Algorithm Project: Update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder [193]
2. Practice Parameters for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (Birmaher et al, 1998a)[44]
3. National Institute for Clinical Excellence guidelines for Depression in Children and young people[194]
4. Practice Parameter for Use of Electroconvulsive Therapy with Adolescents[171]

ASSESSMENT

The assessment process not only involves establishing the diagnosis, but it also should take into consideration, factors like comorbidity, family discord, family psychopathology, risk to life of patient, dysfunction etc. It also involves establishing a good therapeutic alliance with the patient and family members and making decision about treatment setting and patient's safety. In the following section all these issues are discussed. The most important aspect of assessment is that the clinicians understanding of the fact that assessment is not a one step process, but it is a continuous process and patient should be assessed regularly, as per the need and phase of the treatment.

1. PERFORM A DIAGNOSTIC EVALUATION

Patients with depressive symptoms should be evaluated thoroughly to determine whether a diagnosis of depression is warranted and for the presence of other psychiatric or general medical conditions. The complete psychiatric evaluation should include a history of the present illness and current symptoms; a psychiatric history, including symptoms of mania or hypomania as well as a treatment history that particularly notes current treatments and responses to previous treatments; a general medical history and history of substance use disorders; a personal history (e.g., psychological development, response to life transitions, and major life events); a social, educational, and family history; a review of the patient's medications; a review of cardiovascular, pulmonary, neural systems etc; a mental status examination; a physical examination; and diagnostic tests as indicated. In general, for identification of depression in children and adolescent it is better to collect information from various sources, i.e., patients self report, parental, peer, sibling and teacher report and

observation during the clinical interview.

The child and parents or other caregivers can be interviewed separately and also together. Usually multiple interviews are required to get the full picture and collect the information from all possible sources. Wherever possible, developmental perspective should be taken into consideration play techniques can be used as part of assessment of mental status assessment. It is reported that depressed preschoolers show significantly less symbolic play and greater engagement in nonplay behavior, such as exploration of toys and interaction with the examiner, than healthy and nondepressed comparison groups. Depressed children also demonstrate less coherence in their play.

2. DIFFERENTIAL DIAGNOSIS, COMORBIDITY, PHYSICAL EVALUATION AND INVESTIGATIONS

As discussed earlier, comorbidity is very common in childhood and adolescent depression. It is very important to identify and distinguish the comorbid condition from depression, as these can have management implications and can also predict the prognosis in terms of recurrence of depressive episodes, suicide attempts, response to treatment and the utilization of mental health services. Among the preschool depressed children, the common comorbid conditions include attention deficit hyperactivity disorder (42 %), oppositional defiant disorder (62%) and both the above disorders (41%) and only 28 % had comorbid anxiety disorders (Luby et al, 2003). The most common comorbid conditions in adolescents include anxiety (30–75%), conduct disorder (10–80%), substance abuse (20–30%) and personality disorder (60%)[19,54].

Further, as is commonly seen in adults, many psychiatric and medical conditions may mimic depression in children also. During the physical evaluation the clinician should remember to evaluate for the presence of thyroid dysfunction, anemia, chronic fatigue syndrome etc, as these may mimic depression. Major depression can also occur in the presence of chronic medical disorders like, diabetes and systemic lupus. Some of the medications have also been reported to cause depression. Wherever, there is doubt about any physical illness, help of paediatrician and other specialist should be taken.

Identifying depression in the presence of a medical disorder can be difficult when the medical disorder causes sleep disturbance, appetite change, somatic symptoms, and loss of energy. However, feelings of guilt, worthlessness, hopelessness, and thoughts of suicide are unlikely to be due to a medical disorder and strongly suggest the presence of major depression.

4. ASSESSMENT OF SUICIDE RISK

Assessment of suicidal risk in children and adolescents is one of the most important aspects of management of depression. It involves direct and systematic inquiry about the presence or absence of suicidal ideation, specific plans for self-injury, and any history of actual self-harm or overt threats or gestures. It is a common myth that talking about suicide may be harmful (or ''give the child ideas''), but it is not true. Empirical data suggest that such inquiry into suicidal ideations if done carefully and tactfully can in fact help to reveal previously unsuspected suicidal ideation or acts. For prepubertal children, inquiry about suicide must be done in developmentally appropriate terms with attention to a child's concepts of death, as times the child may not view death as irreversible. In fact, inability to conceive death as irreversible may, in some cases, may increase the risk of a suicide attempt. Questions may begin, with questions like, *"Do you ever feel things are so bad that you wish you were dead?", "Do you ever feel like wanting to hurt yourself or do anything to kill yourself?".* If patient responds in yes, further inquiry can include questions like, *"Have you ever done anything to hurt yourself or to try to kill yourself?".* If response to such question is in yes, further inquiry should focus on about what was done and the outcome of such an act along with any possible precipitants and context of the ideation or action.

It is also important to assess the motivation and intent of any attempt if present in the past and the clinician should remember that it is not the method per se, but the subject own understanding of lethality which is more important. History of multiple attempts in the past, persistent suicidal ideation, and high intent are associated with repetition of attempts and completion of suicide. Other factors which should be taken into consideration

are psychological and interpersonal situation, family and interpersonal relations, comorbidity, chronicity of depression, risk taking behaviours, impulsivity, aggression and hostility, presence of auditory hallucinations commanding the child to hurt or kill him or her, history of physical and sexual abuses and failure – exams and love, grief.

Last but not the least, queries about availability of lethal means (potentially lethal drugs, access to guns) must be made. The availability of firearms in particular magnifies the risk of completed suicide, because attempts with firearms are far more lethal than most other means used by adolescents.

4. EVALUATE THE DYSFUNCTION

It is also very important to evaluate the level of dysfunction in terms of academic performance, family functioning and peer relationship. Functioning can be tracked using scales such as, The Children's Global Assessment Scale[95] or The Global Assessment of Functioning[23].

5. SUPPORT SYSTEM AND AVAILABLE RESOURCES

Understanding of child's support system is very important as it forms the backbone of the treatment plan to be carried out. While evaluating the support system, it is important to remember that, it is not the number which matters, but it is the comfort level of the child with that adult which matters. At times, although both the parents may be available, but one may be overcritical and other may be sulking his/her guilt. In such cases it is important to educate the parents, and they should be evaluated for psychiatric morbidity.

6. DETERMINE A TREATMENT SETTING

The treatment of depressive youth should be provided in the least restrictive treatment setting that is safe and effective for a given patient. Selection of treatment setting should take into consideration: patient's clinical picture including severity of symptoms, parents' support, motivation for treatment, and family's ability to keep the patient safe. Patients who exhibit suicidal or homicidal ideation, intention or a plan require close monitoring. Hospitalisation is usually indicated for patients who are considered to pose a serious threat of harm to themselves or others. The patients who should be considered for inpatient setting treatment are shown in table-3.

Table-3: Indications for admission in children and adolescents with depression

1. Those who express suicidal ideas of a definite sort, or who have made a attempt of suicide
2. Those who harm themselves, or threaten to harm others
3. Subjects who have problems with treatment compliance or delivery, leading to unduly protracted treatment
4. Those who require electroconvulsive therapy
5. Those who neglect themselves substantially, particularly their fluid intake
6. Those who require removal from a hostile social environment

7. ESTABLISH AND MAINTAIN A THERAPEUTIC ALLIANCE

An effective therapeutic alliance should be fostered very early in treatment, to maintain patient and family involvement over the course of treatment. Regardless of the treatment modalities ultimately selected for patients, it is important for the clinicians to establish a therapeutic alliance with the patient. Depression is often a chronic condition and it requires patients to actively participate and adhere to treatment plans for long periods. For these reasons, a strong treatment alliance is crucial. The most important component of the therapeutic alliance is that clinician should pay attention to the concerns of patients and their families as well as their wishes for treatment. Management of the therapeutic alliance should also include awareness of transference and counter-transference issues, even if these are not directly addressed in treatment.

8. MONITOR THE PATIENT'S PSYCHIATRIC STATUS AND SAFETY

In the due course of treatment, different features and symptoms of the patient's illness may emerge or subside. Monitoring the patient's status for the emergence of changes in destructive impulses towards self or others is especially crucial. Additional measures such as hospitalization or more intensive treatment should be considered for patients found to be at higher risk. Significant changes in a patient's psychiatric status or the emergence of new symptoms may warrant a diagnostic re-evaluation of the patient.

9. PROVIDE EDUCATION TO THE PATIENT AND, WHEN APPROPRIATE, TO THE FAMILY

Psychoeducation is the most important component of management of depression in children and adolescents. It not only helps the patients and their families, but it also helps the clinician. It is seen that educating the patient and family make them become informed partners in the treatment team and greatly improves the treatment adherence in youth. Education about depression also helps in formulating a treatment plan, decreases parental self-blame *("I'm not a good parent")* and blame of the child (*"He's manipulative," or "He's lazy"*). Furthermore, it appears that educating parents about their child's depression helps them identify their own depressive symptoms and potential need for treatment. Topics should include the signs and symptoms of depression, the role of psychiatric medication, common misconceptions about medications, side effects of medication, lag period with medication before improvement, importance of compliance, warning signs of worsening or relapse and recurrence, impact on school attendance and academic functioning, the role of the parents and teachers in recovery, and impact on peer and family relationships.

Education should be offered to all family members because the symptom of depression (e.g., lack of interest, fatigue, irritability, and isolation) can affects each of them. At times, family members and friends take the patient's behaviors personally or otherwise become emotionally overinvolved, causing more stress, guilt or anger for the patient to cope with. Supportive and understanding relationships improve the patient's and family's global functioning and treatment outcome. Regardless of whether interpersonal circumstances precede or follow onset of the depressive episode, a reduction in these problems is important in the resolution and prevention of future episodes.

10. ENHANCE TREATMENT ADHERENCE

The successful treatment of depression requires close adherence to treatment plans. There is evidence that depressed adolescents often do not seek treatment. Hence, it is very important for the clinician to educate the patient and family about the need of regular follow up and drug compliance.

10. WORK WITH THE PATIENT TO ADDRESS EARLY SIGNS OF RELAPSE

Fluctuation of symptoms is common in depression and patients and their families should be educated about the significant risk of relapse. They should be educated to identify the early signs and symptoms of new episodes. Families should also be asked to seek adequate treatment as early in the course of a new episode as possible to decrease the likelihood of a full-blown relapse or complication.

ACUTE PHASE TREATMENT

The goal of acute phase treatment is to achieve remission. Treatment should generally result in resolution of symptoms, reduction of dysfunction and improvement in quality of life of the child, improvement of family functioning.

Selecting initial treatment modality is dictated by several factors, including severity of depression, number of prior episodes, chronicity of depression, subtype, age of the patient, contextual factors like family conflict, academic problems and exposure to negative life events, compliance with treatment in the past, previous response to treatment, and patient's and family's motivation for treatment and response to a particular treatment in family member. However, one of the most important factors in selecting a particular treatment modality is family and patient's preference. It is seen that at times a socially phobic patient may refuse group therapy and an anxious parent or patient may refuse medications as the first line of treatment, so alternate treatments may be required. Besides the patient, family and clinical variables it is also important to take into consideration the

clinicians factors before determining the initial treatment modality. The clinician factors include clinician availability, motivation, and expertise with a specific therapy. Hence, the decision to initiate medication versus specific psychotherapy should be made jointly by the clinician and adequately informed parents (guardians) with assent from the child.

With the available evidence, **psychotherapy appears to be a useful initial treatment for mild to moderate depression**. Selection of specific type of psychotherapy will depend on clinician's experience and comfort along with the patient's needs. Evidence suggests that CBT and IPT are effective treatments, at least for mild to moderate depression. CBT has yielded response rates similar to those of medication and appears superior to supportive psychotherapy and systemic behavioral family therapy (Birmaher et al., 2000; Brent et al., 1997; Compton et al., 2004). CBT should be preferably used in children and adolescents with cognitive distortions and comorbid anxiety disorders. IPT may be beneficial in presence of stressors like separation from parents, authority concerns with parents and teachers, loss or death of relatives or friends etc. In a country like India, where few clinicians have expertise and time to carry out CBT or IPT, supportive psychotherapy may also be useful.

Antidepressant medications may be used for children and adolescents with **moderate depression in which psychotherapy is not feasible, severe depression with or without psychotic symptoms** and **depression that fails to respond to an adequate trial of psychotherapy**. For patients requiring pharmacotherapy, SSRIs, especially **fluoxetine (first choice), sertraline or citalopram** can be considered. However, before selecting any antidepressant, parents and other caregivers must be provided information about the potential risks and benefits and informed consent to start the medication must be taken. Parents and patient should be explained about side effects, dose, the timing of therapeutic effect, and the danger of overdose. Patients who are at risk of committing suicide, it is recommended that parents should be given the responsibility for storing and administering medications, especially during the acute and during the first 2 to 4 months after complete remission. It is also important that parents need to be made aware of possible role of SSRI with regard to suicidality and they should be asked to be vigilant and should monitor the patent's behaviour. At present, there is no indication for baseline laboratory tests before and during the administration of SSRIs.

At present there is maximum support for the efficacy of fluoxetine in treating depression in children and adolescents, and it is the only antidepressant to show positive efficacy in more than one acute trial. Hence, fluoxetine should be the first line treatment unless reasons like potential drug interactions, family resistance, prior lack of response with an adequate dose and trial preclude its use. In such cases, sertraline and citalopram can be considered.

When used, SSRIs should be started in low doses (usually half the starting dose of adults) and gradually titrated to achieve a balance between symptom control and avoidance of side effects. When used, fluoxetine can be started in the dose of 10 mg daily and this can be increased to 20 mg daily after 1 week if there are no side-effects. There is little evidence regarding the effectiveness of doses higher than 20 mg daily.

It is important to remember that depression in children and adolescents often occurs in psychosocial context and hence besides using antidepressants associated environmental and social problems should be addressed with supportive measures. Combined treatment increases the likelihood of remission, but also increases self-esteem, coping skills, and adaptive strategies and improving family and peer relationships.

Further in case of psychotherapy or pharmacotherapy, specific interventions should be provided to parents and other caregivers to help them effectively manage the child's irritability, defiance, isolation, or other behavioral problems. If any of the parent or significant family member has any mental problem, it should be addressed.

While patient is treated with antidepressants it is advisable to see the patient once in 1-2 weeks, because this will help the clinician to monitor the patient's depression status (improvement or worsening), emergence of suicidality if any, monitor bothersome adverse effects and to adjust dose accordingly and increase patient adherence to treatment. During follow-up it is recommended that severity of depression should be monitored objectively using various clinicians and self rated scales.

There is no consensus with regard to an adequate trial in children and adolescents, and it is extrapolated from the adult data. Once an antidepressant is started, patients should be treated with adequate and tolerable doses for at least 4 to 6 weeks. If patient shows no response, by 4 weeks, the clinician should increase the dose to maximum tolerable dose, with close monitoring of side effects. If patient shows partial response with minimal or no side effects by 4-6 weeks, the clinician should wait till 8 weeks and increase the dose to maximum tolerable dose before considering failure of response. However, these recommendations should be applied cautiously, because the SSRIs possess a relatively flat dose-response curve, suggesting that maximal clinical response may be achieved at minimum effective doses. Therefore, adequate time should be allowed for clinical response, and frequent, early dose adjustment should be avoided.

CONTINUATION TREATMENT PHASE

Although there is not much data about treatment of depression during the continuation phase, but taking into consideration the high rate of relapse and recurrence of depression, continuation therapy is recommended for all patients for at least 6 to 12 months after remission. During the continuation phase, patients typically are seen at least monthly, depending on clinical status, functioning, support systems, environmental stressors, motivation for treatment, and the presence of comorbid psychiatric or medical disorders. If patient was initially treated with psychotherapy only, it must be continued. The frequency of sessions can vary depending on the need of the patient. If patient was initially treated with antidepressants then the dose which was effective in the active phase should be continued. In addition, patients who were treated with antidepressants and nonspecific psychotherapy during the active phase can be provided specific psychotherapy during this phase to address the antecedents, contextual factors, environmental stressors, and intrapsychic conflicts that may contribute to a relapse. At the end of the continuation phase, if maintenance treatment is not needed, medications should be discontinued over a 6-week period or more to avoid withdrawal effects. Although fluoxetine has a long elimination half-life, it is also better to taper it as well. Before tapering off medication, tapering schedule, withdrawal symptoms and relapse must be discussed with the patient and the family. Because the chances of relapse are very high during the first 8 months after stopping treatment, patients should be seen every 2 to 4 months during this period. If depression recurs, then prompt treatment with the previously effective medication should be reinitiated.

MAINTENANCE TREATMENT PHASE

Once the patient has been asymptomatic for approximately 6 to 12 months, the clinician must decide whether maintenance therapy is indicated or not. Besides the number of previous episodes, severity of the present and previous depressive episodes (e.g., suicidality, psychosis, functional impairment), presence of comorbid disorders, side effects of continued treatment, and patient's and family preference dictates maintenance treatment. Environmental factors, such as family stability (e.g., divorce, illness, job loss, or homelessness), family psychopathology, appropriateness of school placement and contraindications for treatment, also must be taken into consideration before deciding about the maintenance treatment. As there is no sufficient data about the maintenance treatment in children and adolescents, data from adult literature should be extrapolated to decide about the definitive indications for maintenance treatment. It is recommended that patients with two (if episodes are characterized by psychotic symptoms) or three episodes of depression, severe suicidality, severe impairment during the episodes, family history of affective disorders and history of treatment-resistance should receive maintenance treatment.

The optimal duration of maintenance medication has not been established in adults or children and adolescents, but depending on risk factors, is generally believed to be between 3 years to lifetime. The initiation and duration of maintenance treatment should be a collaborative decision of patient, family and clinician with appropriate consideration of patient and family's preference as well as the risk factors for recurrence.

Unless there is a contraindication, the psychotherapeutic or pharmacological treatments that were efficacious to induce the remission of the acute episode should be used for maintenance therapy. It is important to note that the long-term effects of antidepressant medications on the maturation and development of children have not

been studied. The clinician and the patient's family should weigh the risks and benefits of maintenance antidepressants against the possible consequences of relapses.

During the maintenance phase patient should be monitored at least monthly or quarterly, depending on the patients' clinical status, functioning, social support and environmental stressors.

PARTIAL OR NON-RESPONSE TO INITIAL TREATMENT

Again there is no evidence base about what to do in children and adolescent who don't respond to an adequate trial of SSRI, but with extrapolation of adult data it can be suggested that a second SSRI should be tried in such cases. If patient was initially treated with fluoxetine, then it can be stopped immediately and the second antidepressant can be built-up slowly; but if initially the patient was treated with some other SSRI, then cross tapering should be done. If the patient experienced intolerable side effects with SSRI (e.g., nausea, excessive restlessness, agitation) during the first trial, then the second SSRI should be started at lower doses. If patient was initially treated with psychotherapy, and doesn't show any response, then he should be either started on an SSRI or alternate form of psychotherapy should be considered.

If the patient shows partial response to the initial SSRI trial, augmentation strategy can be used. The potential advantages of augmentation versus switching to another antidepressant monotherapy include no need for discontinuation of initial antidepressant, less lag time for response, partial responders continue to receive treatment without interruption, and treatment of breakthrough symptoms is possible. The best augmenting agent for children and adolescents who fail to respond to SSRIs or are partial responders remains to be determined. Based on adult data and expert opinion, augmentation may be a useful strategy for youths who have shown initial response with optimal dosing, but who have not achieved remission and augmentation recommendations from adult data can be extrapolated.

NON-RESPONSE TO SECOND SSRI

If the patient fails to respond to second SSRI trial, then it is important to re-evaluate the diagnosis, comorbidity, non-compliance and other psychosocial factors which may be contributing to non-response. The adequacy of psychotherapeutic interventions should also be checked and all the possible modifications which can improve the condition should be made. With all these measures, if it is clear that diagnosis is clear and other contributing factors have been addressed and patient still fails to respond to second SSRI, based on adult data, it is recommended to switch to venlafaxine, bupropion or mirtazapine.

WHEN TO USE ECT

ECT is considered in an adolescent with depression, if he/she must meet the following criteria:

1. Severe, persistent major depression with or without psychotic features, including catatonia

2. The patient's symptoms are severe, persistent, and significantly disabling which may be in the form of life-threatening symptoms such as the refusal to eat or drink and severe suicidality

3. Failure to respond to at least two adequate trials of appropriate antidepressant agents accompanied by other appropriate treatment modalities.

4. ECT may be considered earlier in cases if adequate medication trials are not possible because of the patient's inability to tolerate the antidepressant, the adolescent is grossly incapacitated and thus cannot take medication, or waiting for a response to a psychopharmacological treatment may endanger the life of the adolescent.

CONTRAINDICATIONS

As such there are no absolute contraindications to the use of ECT in adolescents. Tumors of the central nervous system associated with elevated cerebrospinal fluid levels, active chest infection, and recent myocardial infarction may be considered relative contraindications in adolescents.

CLINICAL FEATURES THAT REQUIRE SPECIAL ATTENTION

Suicidal Ideation and/or Suicide Attempts: In general, the treatment of suicidal youth is similar to that for non-suicidal youth, except for additional focus on assessment, monitoring, and amelioration of suicidality. If the risk of suicide is high, admission to an inpatient should be considered strongly and high risk management should be implemented. If admission is denied, then the family should be advised to implement the high risk management at home and all lethal agents, especially firearms and toxic medications, should be removed from the patient's home. It is commonly seen that family conflict, hopelessness, and cognitive distortions are frequently present in suicidal adolescents, hence, initial treatment should include family therapy and education and other psychosocial interventions. SSRIs may be prescribed if there is significant impairment that reduces the patient's capacity to benefit from psychotherapy, or if the patient worsens or fails to improve with psychotherapy alone.

Psychotic Depression: As is the case in adult psychotic depression, antipsychotics should be added to antidepressant for psychotic depression. There is no data in adolescents which can specifically help to select a particular antipsychotic, but atypical antipsychotics should be preferred. Because antipsychotics pose the risk of tardive dyskinesia, weight gain, hormonal changes and long term effects have not been evaluated in this population; it is advised to taper off antipsychotics following remission of psychotic symptoms. It is important to remember that presence of psychotic symptoms in depression is an indicator of possible development of bipolar disorder, and clinicians should be alert to this possibility, particularly if antidepressants are prescribed.

Atypical Depression: Psychotherapy and pharmacotherapy are used frequently, although no psychotherapy or pharmacotherapy studies on atypical depression in children and adolescents have been published.

Treatment-Resistant Depression: If an adolescent presents with treatment-resistant depression, proper evaluation of treatment failure should be done, which should include assessment of dose of drugs used in the past, length of drug trial, length of psychotherapy, compliance with treatment, comorbidity with other psychiatric disorders (anxiety, dysthymia, substance use, and personality disorders), comorbid medical illnesses, undetected bipolar depression, exposure to chronic or severe life events, such as sexual abuse, that may require different modalities of therapy. There is meager evidence that adolescents with treatment resistant may respond to ECT.

Because of lack of data, several psychopharmacological strategies have been recommended for adults with TRD may be applicable to youth: optimization (extending the initial medication trial and/or adjusting the dose), and switching to another agent in the same or a different class of medications, augmentation or combination (e.g., lithium, T3). Each strategy should be implemented in a systematic fashion, education of the patient and family, and support to reduce the potential for the patient to become hopeless.

Comorbid anxiety disorders: Anxiety disorders or anxiety symptoms are frequently associated with depressive disorders, and treatment with SSRIs tends to address both sets of symptoms. It has also been seen that patients with comorbid anxiety disorders respond better to CBT.

Comorbid ADHD: Treatment of depression with comorbid ADHD is very challenging and selection of treatment modality with depend on the relative severity of both the conditions. If ADHD is more severe than depression, than preferably psychostimulant (Methylphenidate) should be started first. If both depressive and ADHD symptoms improve with stimulant, then continuation treatment with psychostimulant must be done. If depression doesn't respond to stimulant, then it is advisable to substitute with a SSRI. Once depression improves with SSRI it is advisable to re-evaluate the patient for ADHD symptoms and if they are present patient should be treated according to guidelines for ADHD.

However, if depression is more severe, it should be treated before ADHD. If both depressive and ADHD symptoms adequately improve, then the same treatment should be continued. If only depressive symptoms improve and ADHD symptoms continue then the patient should be treated according to guidelines for ADHD.

Figure -1: Treatment algorithm of Depression in children and adults

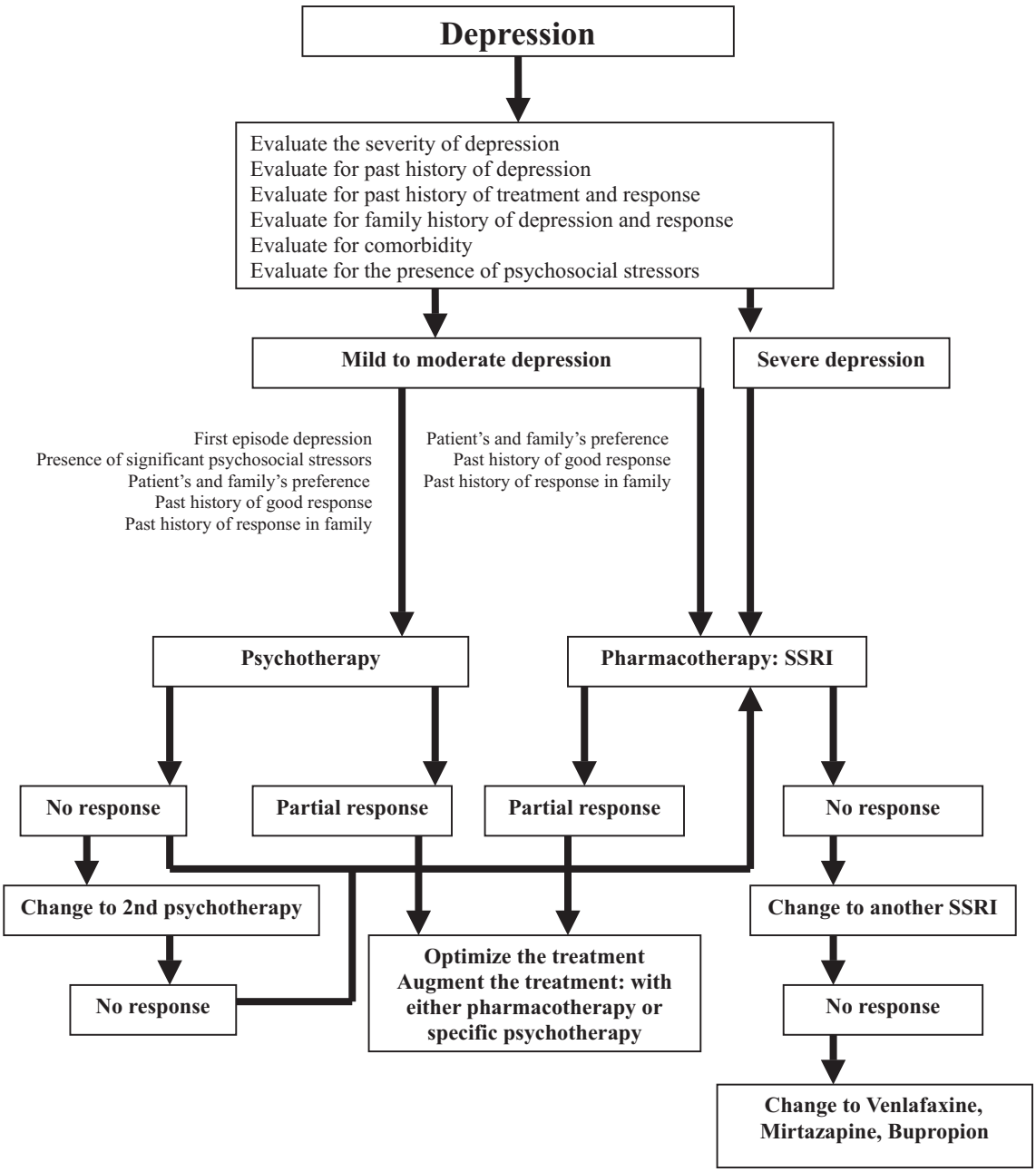
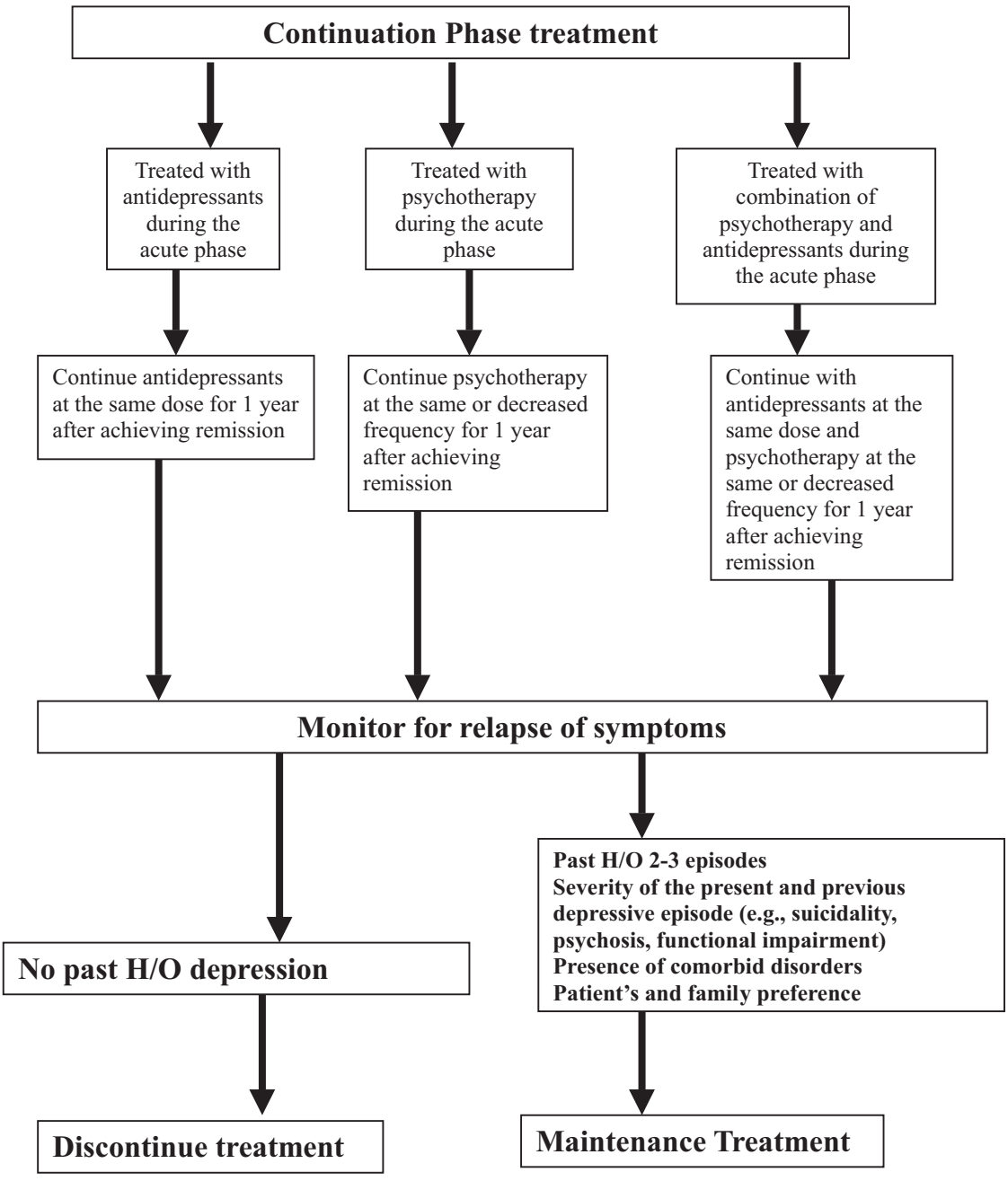


Figure -2: Treatment algorithm for continuati on phase of depression in children and adults



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