Child and adolescent depression: short-term treatment effectiveness and long-term opportunities

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ABSTRACT As with adult major depressive disorder (MDD), child and adolescent MDD is characterized as a common, chronic and recurrent disorder. It is also associated with short- and long-term functional impairment, morbidity, and mortality. Effective treatments, both psychotherapeutic and pharmacotherapeutic, are available for the short-term treatment and management of youth with MDD. However, to date, there are no data on the long-term treatment and management of children and adolescents with MDD and how long-term treatment may affect the outcomes of either high-risk or already affected youth. Understanding the long-term consequences of MDD during youth is as important as understanding how to treat a single episode of depression.

Available data on the pharmacotherapeutic and psychotherapeutic options are discussed. In general, tricyclic antidepressants (TCAs) are not as effective for the treatment of youth with MDD as adults with MDD. The selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective in children and adolescents with MDD and non-obsessive compulsive anxiety disorders. The serotonin and norepinephrine reuptake inhibitor (SNRI), venlafaxine XR, has been shown to be effective for the treatment of generalized anxiety disorder in children and adolescents.

Understanding the long-term clinical consequences of depressive disorders in youth may provide opportunities for better intervention across the clinical course of illness. Early recognition, diagnosis and adequate treatment of 'high-risk' youth with subsyndromal depressive symptoms, treatment of acute episodes of depression to prevent 'kindling', and aggressive prophylaxis have the potential to improve the mental health of youth throughout their lives.

Key words: youth, MDD, GAD, pharmacotherapy, psychotherapy

Introduction

Current estimates of point prevalence or one-year prevalence for major depressive disorder (MDD) are approximately 1% to 2% in pre-pubertal children and 2% to 5% in adolescents (Fleming and Offord, 1990). Indeed, 14% to 25% of recent cohorts experience at least one major depressive episode during adolescence (Kessler et al., 1998; Lewinsohn et al., 1998a). There appears to have been a secular increase in the rate of depression in youth over the past 30–40 years; however, this may well have reached a plateau since the available data are based on cohorts born before the 1980s (Ryan et al., 1992; Lewinsohn et al., 1993; Kovacs and Gatsonis, 1994; Kessler et al., 1998). During and following a major depressive episode, youth experience impairment in psychosocial functioning at school, with friends and with family

(Puig-Antich et al., 1985a,b, 1993; Rao et al., 1995). Youth with MDD, which is associated with a greater number or longer duration of episodes of MDD, have elevated rates of pregnancy and are at increased risk of suicide (Ryan et al., 1987; Weissman et al., 1999a). The majority of clinic-referred depressed youth have recurrent episodes. The clinical picture of depression both in children and youth is very similar to that seen in adult MDD, particularly when examining the rate of both criterion and non-criterion symptoms of the disorder. However, adolescents have a higher rate of endogenous/melancholic subtype of depression, and have a higher rate of suicide attempts with a greater lethality of suicide attempts than observed in prepubertal children (Ryan et al., 1987). Youth with MDD, like adults with the disorder, frequently have

co-morbid disorders including anxiety disorders, dysthymia, disruptive disorders and substance abuse (Angold et al., 1999).

Adolescent depression appears to be continuous with adult depression – depressed adolescents grow up to be depressed adults (Ryan et al., 1987; Rao et al., 1995). Whether or not depression in childhood is continuous with that in adulthood is, at present, not entirely clear. Some limited data suggest relatively less or perhaps very little continuity from childhood depression to adult depression, but limitations in the measures and designs of the few available studies make this a difficult question to answer (Harrington et al., 1990; Weissman et al., 1999b; Weissman, 2002). Pubertal maturation rather than age *per se* seems to be associated with both an increase in the rate of MDD and a shift from an approximately 1:1 female to male ratio to a more adult-like female excess (Angold et al., 1998).

For youth with MDD, the risk for bipolar disorder appears to be high – up to 30% or more in some samples of clinic-referred youth (Geller et al., 1994). While this may appear to be at variance with the population data on the rate of bipolar disorder in adolescents (Lewinsohn et al., 1995), MDD in youth has a significantly higher risk for eventual bipolar disorder than MDD with later onset. This may be explained by the fact that bipolar disorder has an earlier average age of onset than unipolar disorder (new onset of bipolar disorder becomes rarer at an older age than new onset of unipolar depression).

The incidence of MDD in children and adolescents, who are first-degree biological relatives of an adult with MDD, is higher than for youth of unrelated adults (Weissman et al., 1984; Puig-Antich et al., 1989; Thapar and McGuffin, 1994, 1996; Williamson et al., 1995; Neuman et al., 1997; Silberg et al., 1999; Klein et al., 2001). It appears that the risk factors (such as perinatal insults, motor skills deficits, caretaker instability) associated with MDD in youth are different from those associated with the adult form of the disorder (Jaffee et al., 2002). Although it has been suggested that prepubertal depression may be relatively more environmental (Thapar and McGuffin, 1994, 1996; Thapar et al., 1998) than genetic, the study focused on the temporal concordance of depression in prepubertal siblings. This may have introduced a bias towards a greater influence of environmental factors on depressive disorders than looking at the lifetime

incidence of depression during puberty (Thapar and McGuffin, 1994, 1996; Thapar et al., 1998). Like MDD throughout the lifespan, MDD in youth has both genetic and environmental factors that contribute to the disorder. Undoubtedly, some of these factors are common to MDD in youth or adulthood, whereas others may be unique or of greater importance during different stages of development (childhood through to adulthood).

Pharmacological treatment

In adult MDD, there are numerous well-replicated studies showing therapeutic efficacy of a number of pharmacological agents, including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Both TCAs and SSRIs have been shown to have approximately equivalent overall efficacy and both are superior to placebo. However, it has recently been suggested that serotonin and norepinephrine reuptake inhibitors (SNRIs) may have greater efficacy than SSRIs (Thase et al., 2001). In children and adolescents, SSRIs have been shown to have efficacy in the treatment of acute MDD, with an efficacy profile similar to that seen in adults. In contrast, TCAs appear to have little or no efficacy in the treatment of children and adolescents with MDD. To date, there are few data on other classes of antidepressants for the treatment of MDD in youth.

The efficacy of TCAs in children and adolescents with MDD has been studied (Birmaher et al., 1996a; Ryan et al., 1998). Results have been reported of an additional eight-week, double-blind study comparing the efficacy of paroxetine with placebo and imipramine for the treatment of adolescent depression (Keller et al., 2001). In aggregate, across all available studies, 500 youth have been included in randomized, double-blind, controlled studies of children or adolescents with MDD, which have compared TCAs with placebo. The results from these studies suggest there is no evidence of separation of efficacy between TCAs and placebo. This does not preclude the possibility that TCAs may have some efficacy in this population. However, in the treatment of youth with MDD, it is statistically improbable that TCAs would exhibit an efficacy level equivalent to that observed in the treatment of MDD in adulthood.

Data on the efficacy of SSRIs in depressed youth are now available from several NIMH-funded and industry-funded short-term studies. One of the first

studies of the SSRI, fluoxetine, failed to show separation of efficacy between fluoxetine and placebo (Simeon et al., 1990). However, the placebo response rate in this study was high, which may have contributed to the lack of separation in efficacy between active drug and placebo (Simeon et al., 1990). Intravenous administration of clomipramine, which acts primarily as a serotonin reuptake inhibitor (especially when given intravenously), in adolescents with MDD ($n = 16$) was shown to have greater efficacy compared with placebo (Salleee et al., 1997). Two additional studies, an NIMH-funded single-site study (Emslie et al., 1997) and an industry-funded multi-site study (Emslie et al., 2000), have also shown that fluoxetine has greater efficacy than placebo in children and adolescents. Paroxetine has also been shown to be more efficacious than placebo on measures of recovery and depressed mood; however, there was no statistical difference observed on the pre-planned Hamilton Rating Scale for Depression (HAM-D) aggregate score (Keller et al., 2001). This is in contrast to the comparison of imipramine and placebo from the same study, in which imipramine was shown to have no greater efficacy than placebo on any measure (Keller et al., 2001). In a single study of citalopram (Wagner et al., 2001) and a pre-planned aggregation of two co-ordinated studies of sertraline (Wagner and Wohlberg, 2002), both citalopram and sertraline were shown to have greater efficacy than placebo on the pre-planned outcome measures. In aggregate, these studies enrolled 1,012 children and adolescents with MDD with approximately equal numbers of patients receiving an SSRI or placebo. Overall, these results suggest that SSRIs are effective in child and adolescent depression and the effect size of the efficacy of the SSRI compared with placebo appears similar in youth to that found in recent studies of adult MDD. The limited number of studies in the treatment and management of children and adolescents with MDD makes it all the more important that all data from such studies are available to the scientific and medical professions. There have been occasions where the reporting of results from industry-supported studies that failed to show differences between active medication and placebo has been delayed. It is important to realize that even for an effective agent or class of agents, it is normal to have some studies that do not show separation of efficacy between active treatment and placebo. There are many errors that can

lead to a type II statistical error (failure to demonstrate a real difference between treatments), such as anything that adds 'noise' to assessments or ongoing evaluations. Thus, the ability to aggregate all data could lead to better-targeted treatment; this will almost certainly require trust in an independent third party to hold and analyse the aggregated data. The potential value of the knowledge that might be gained from such an aggregation would be well worth the effort.

Non-obsessive compulsive anxiety disorders (social anxiety disorder, separation anxiety disorder, generalized anxiety disorder) and MDD appear to share the same genetic underpinnings (Kendler et al., 1995) and in many youth and adults, the anxiety disorder precedes the depressive disorder. Therefore, the response of anxiety disorders to treatments for MDD is interesting as we consider the potential for secondary prevention. Recently, fluvoxamine was shown to be more effective than placebo in the treatment of children and adolescents with non-OCD anxiety disorders (Walkup et al., 2001). The change in total score on the Pediatric Anxiety Rating Scale (PARS) was significantly greater ($p < 0.001$) for youth in the fluvoxamine group compared with those in the placebo group (Figure 1). A total of 76% of youth in the fluvoxamine group were classified as responders on the Clinical Global Impressions-Improvement (CGI-I) scale (score (4) compared with 29% in the placebo group ($p < 0.001$) (Walkup et al., 2001).

In a recent study of venlafaxine XR, children and adolescents with generalized anxiety disorder (GAD; $n=158$), aged between 6 and 17 years, were randomized to receive venlafaxine XR or placebo for ≤ 8 weeks. Children and adolescents receiving venlafaxine XR showed a mean decrease of 18.6 points on the Columbia Kiddie Schedule for Affective Disorders and Schizophrenia (C-KIDDIE-SADS) total score for GAD compared with a reduction of only 12.4 points for those receiving placebo (Kunz et al., 2002). Similarly, response rates as determined by CGI-I score > 3 were significant ($p = 0.004$) for children and adolescents receiving venlafaxine XR (64%) compared with those in the placebo group (40% [Figure 2]) (Kunz et al., 2002).

Psychotherapeutic treatment

In youth, anxiety disorders and MDD appear to respond equally well to cognitive behavioural therapy (CBT) (Labellarte et al., 1999) when delivered either

Figure 1. Change in total score on the Pediatric Rating Scale for youth receiving fluvoxamine compared with those in the placebo group (* $p < 0.001$). Adapted from Walkup et al. (2001).

Figure 2. Response rate, as determined by CGI-I score >3, for children and adolescents receiving venlafaxine XR compared with those in the placebo group. CGI-I: 1 = very much improved; 2 = much improved (* $p = 0.004$). Adapted from Kunz et al., 2002.

individually or in a group setting (Birmaher et al., 1996b; Harrington et al., 1998a,b; Lewinsohn and Clarke, 1999). Some of the studies assessing the efficacy of psychotherapy have used a wait-list control. Given the relatively high response rate seen in the placebo arm of randomized controlled medication trials, psychotherapy studies in which wait-list controls are utilized must be viewed as relatively non-specific. The high response rates with placebo pills illustrate the fairly large and clinically meaningful effect of the non-specific aspects of treatment; the critical research question is which treatments provide the best

outcomes for patients. Other psychotherapy studies in youth have shown specific efficacy of CBT compared with other 'placebo' psychotherapeutic approaches such as cognitive, family and support therapy, which control for expectancy and contact time effects (Brent et al., 1997). One group has also shown that interpersonal therapy (IPT) in depressed youth may also be efficacious (Moreau et al., 1991; Mufson et al., 1996, 1999). Thus, following age-appropriate adaptations, two psychotherapies that are effective in adult major depression, CBT and IPT appear to be effective in MDD in youth.

Gaps in knowledge of acute and chronic treatment

Recent regulatory changes by the FDA encourage the study of new antidepressant treatments (those compounds that are on patent) in youth. Thus, although results are not yet available, there are ongoing studies of non-SSRI antidepressants in children and adolescents with MDD. However, current regulatory and industry approaches are limited to studies in youth with MDD who are non-suicidal and who do not have treatment-resistant depression. Such studies are all acute (short-term) efficacy studies with or without a six-month to one-year continuation phase for responders. These studies are extremely valuable and the logical choice for the first step in accumulating data on a medication for the treatment of depressed youth. However, these studies provide little or no information about prevention of relapse and recurrence, or the treatment of refractory depression.

Like MDD in adults, MDD in youth is a chronic recurrent disorder so prevention of relapse and recurrence is a high priority. There are three distinct rationales for treating episodes of depression aggressively and providing effective prophylactic treatment options against future episodes:

- Episodes of depression are bad for youth both while in episode and subsequently; depressive illness is associated with suffering, impairment in social interactions at school, with the family and with siblings, and sufferers are at increased risk of suicide, both during the episode and subsequently (Puig-Antich et al., 1985a,b; Brent et al., 1993). Indeed, social impairment frequently continues beyond the episode of depression.
- There may be 'kindling' of future episodes; episodes of depression may increase the risk for future subsequent episodes (Post, 1992; Kendler et al., 2000, 2001). 'Kindling' of MDD in youth must, as yet, be considered a strong hypothesis rather than definitely proven. Effective treatment may improve the future of the individual for many decades to come by breaking the cycle of relapse and recurrence. The earlier treatment is given in the patient's lifespan following early onset of depression, the greater the likelihood of preventing future episodes of depression.
- Similar to the studies in adult depression, short-term treatment probably does not change long-term outcome in youth (Birmaher et al., 2000). We will

need to provide long-term treatment approaches to effectively change the long-term outcome. There are limited data suggesting that extended treatment with fluoxetine may decrease the recurrence rate during the extended treatment phase (Emslie and Mayes, 2001).

Currently, there are no data from controlled studies to help us tailor appropriate treatments for youth. There is no research-based method to decide rationally between starting treatment with an antidepressant or psychotherapy in a particular individual, or to choose an optimal treatment algorithm when the first treatment does not work or is only partially effective.

Two ongoing studies will provide data addressing some of these important gaps. The Treatment of Adolescent Depression Study (TADS) is an NIMH-funded, multi-centre study. It is a 12-week, randomized controlled trial of four separate treatment arms in 432 outpatient adolescents, aged 12 to 17 years, with MDD. Subjects across the 11 treatment sites will be randomized either to: (i) fluoxetine 40 mg/day; (ii) CBT; (iii) fluoxetine plus CBT; or (iv) placebo-pill.

The Treatment of SSRI-Resistant Depression in Adolescents Study (TORDIA) is a five-year, six-site study co-ordinated by the University of Pittsburgh. In this study, 400 outpatient adolescents aged 12 to 17 years, in a current episode of MDD and unresponsive to at least six weeks of adequate SSRI treatment, will be randomized to a 12-week trial of either: (i) a different SSRI; (ii) a different SSRI plus CBT; (iii) venlafaxine; or (iv) venlafaxine plus CBT. Results from these studies are eagerly awaited.

So far, we know relatively little about how to prevent first episodes of depression. In one elegant study, Clarke et al. (2001) studied adolescents aged 13 to 18, who were at high risk of developing full MDD because they had (1) subsyndromal depressive symptoms but not full MDD, and (2) a parent who was being treated for MDD or had been treated for MDD over the past year. Those randomized to receive 15 one-hour sessions of group CBT ($n = 45$) showed significant improvement compared with those randomized to usual care ($n = 49$) (Clarke et al., 2001). Survival analysis of incident major depressive episodes over 15 months of follow-up showed a significantly greater advantage of CBT compared with usual care (9.3% versus 28.8% developed MDD in the CBT versus usual-care group, respectively ($p = 0.003$)).

(Clarke et al., 2001). Over the full 24-month follow-up, there was still a significant ($p = 0.005$) difference between the two groups, although somewhat less.

In addition to gaps in knowing how rationally to select a first treatment between known efficacious treatments and in knowing how to select a second treatment when the first is ineffective, we lack critical knowledge of how to use these treatments in clinical practice. Treatments given as part of a highly controlled and well-funded acute study have greater efficacy than the 'same' treatment given by physicians in clinical practice. We have not systematically studied how to provide wide-scale training to clinicians, how to certify them, and how to monitor them over time to ensure that they maintain these skills.

Treatment doesn't work if it is not delivered

Knowing which treatments are efficacious for youth with MDD is only the start. Addressing the problems of getting youth into treatment, keeping them in treatment, and making sure that the treatment they receive is among those therapies with demonstrated efficacy are perhaps the biggest challenges for improving the treatment of depression in youth.

In one study, while 61% of depressed community adolescents received at least some treatment (Lewinsohn et al., 1998b), either involving pharmacotherapy, talk therapy, or some combination, most treatments were unsystematic and brief (22% received one or two sessions of CBT, and the modal length of treatment was seven sessions of CBT) (Lewinsohn and Clarke, 1999) and therefore unlikely to be of maximal benefit to the adolescent. The interval between diagnosis and first treatment of depression (and many anxiety disorders) appears to be approximately 10 years on average (Olfson et al., 1998), which offers enormous opportunity if children and adolescents with mood and anxiety disorders could be identified and treated more quickly. Therefore, the gap between best practice and what is delivered on average is enormous.

Approaches to case finding and patient engagement may need to be targeted to the particular group or subgroup rather than taking a 'one size fits all' approach. For example, in the US, black Americans receive low healthcare services across both physical and mental health, even after controlling for socioeconomic status (Schneider et al., 2002). This does not indicate where the problem is, but does strongly indicate that current approaches to healthcare

delivery are disproportionately less effective for some groups of society, and therefore offer an important target for improvement.

Opportunities

Given the current state of our understanding of mood and anxiety disorders in youth, what opportunities exist and what research might be most helpful to prevent and more effectively treat depression in children and adolescents?

Prevention

Primary prevention in an unselected population requires economical and low-risk methods to change the hazard of subsequent depression. It is possible that CBT approaches could be modified for delivery to children without any depressive symptoms targeting the dysphoric moods that are part of human life. However, there is no evidence that this would prevent depression effectively and it is unclear whether a favourable cost/benefit ratio could be obtained. In an interesting study of first-grade students, interventions targeting risk factors for later adverse psychiatric outcomes (for example, poor academic achievement, aggression and shy behaviours) have been shown to decrease both depressive symptoms and the risk factors associated with subsequent depression (Kellam et al., 1994; Ialongo et al., 1999). However, approaches such as this are most likely to be cost-effective if they achieve sufficient change in the hazard for a wide range of adverse outcomes, not primarily for the change in the rate of depression considered alone.

Adverse life events in youth, including 'loss events' (such as parental divorce), interpersonal traumas and other adversities, increase the risk for depression during adolescence (Williamson et al., 1998) and in adulthood (Kessler et al., 1997). To the extent that societal changes might decrease the rate of adverse life events in childhood (for example, decreasing parental mortality, decreasing child abuse or decreasing divorce), the rate of depression might meaningfully decrease. However, engineering such changes might best be considered as a way to improve the lives of youth and our society overall rather than cost-effective ways of decreasing depression per se. In contrast, whether one would view removing handguns from the home as positive or negative for society, it would almost certainly decrease the rate of suicide in the country; thus, for this related but different psychiatric

issue, one has a very rational and cost-effective primary prevention approach targeted to the particular specific problem.

As demonstrated by the prevention study of Clarke et al. (2001), CBT may have a role to play in decreasing the hazard of subsequent depression in those at particularly high risk (especially if they already have some depressive symptomatology). By extension, other psychotherapeutic approaches, and potentially even medication approaches, might make sense in small selected groups of children who are not yet depressed but at an increased risk because of current symptom picture, other psychiatric disorders known to lead to depression (such as anxiety disorders), or very high family loading for depression.

Ascertainment of depressed youth

Unless we can identify depressed youth, we cannot appropriately deliver treatment to them. Increased ascertainment depends on increasing awareness of the risk for and symptoms of childhood depression in families, in the youth themselves, and in those organizations and individuals who have contact with the youth.

The most significant contact with youth of school age and adolescents includes parents and other family caretakers (for example, custodial grandparents), school personnel, and those involved in religious and civic organizations of which the child is a member. Special populations including the mentally retarded, autistic, adjudicated, or incarcerated populations will require the specific targeting of caretakers for those populations. Children spend large portions of their time with their family and teachers and these individuals may therefore offer the best opportunity for increasing awareness, teaching recognition skills, and facilitation of treatment referrals.

Surprisingly, the primary healthcare system may offer a relatively poor opportunity to increase ascertainment and referral for depressed youth. This is simply because once the child is in school, immunizations are largely over, so many of the youth will have at most an annual physical examination with only a very brief contact with the nurse and pediatrician. The pediatrician's office is filled with health promoting and disorder identification pamphlets, posters, videos, and so forth. However, these may not come to the notice of the attending primary care consultants. Ultimately, screening instruments used in the pediatrician's office approach the quantum minimum of one question per disorder – optimizing that one question and providing

short and clear instructions on treatment once the mood and/or anxiety disorder has been ascertained may be the best primary care opportunity.

Awareness methods may require tailoring to the particular community. Greatly differential ascertainment rates in different ethnic populations in the US suggest that a single blanket approach to all is insufficient.

Keeping children in treatment

Effective treatments do not work optimally without delivering the full dose. Adult data suggests that, after delivering an eight-to-12-week acute treatment, we will need to deliver a six-month-to-one-year continuation treatment and, for recurrent depressions, perhaps years of psychotherapy and/or pharmacotherapy. We need studies to optimize treatment pathways and to understand how to keep the child on the pathway of treatment.

Adolescence is a time of increasing autonomy and control without, in many, fully adult approaches to the behavioural choices made. The irritability and anhedonia that are core symptoms of depression further decrease the chance that the child or adolescent will make the optimum medical decisions for himself or herself. These questions are very researchable but not yet well studied.

To the extent that environment influences the timing of depressive episodes, the shared family environment can be expected to lead to a meaningful temporal correlation in the depressive episodes of family members other than the identified youth, including mothers, fathers and siblings. If this is unrecognized, an adverse impact may be seen on keeping the youth in treatment – for example, when a mother is depressed she is less likely to be effective in getting her child to treatment week after week.

Optimizing the treatment that we deliver

Compared with many other child psychiatric disorders (for example, bipolar disorder), the available treatments for unipolar major depression, both pharmacological and psychotherapeutic, are relatively economical, have low rates of serious adverse events, and are fairly easy to deliver. Nevertheless, considered at the individual level, for some families the out-of-pocket costs are quite significant, the inconvenience to the family in getting treatment for the child may be considerable (for example, the mother has to bring the patient and several young siblings to the office and must take several buses to accomplish that), and the treatment may be perceived

as anything but straightforward (for example, the psychological distress at considering taking medication for years or even a lifetime is considerable in the otherwise healthy youth who prefers feeling as if life is infinite and everything is possible).

If psychotherapeutic treatment must continue for many months or even years for best long-term prophylaxis (the question is open), we may need to think more broadly about how this treatment is delivered and by whom. One possibility would be to teach the parent(s) to provide ongoing 'CBT-like' maintenance to the child with only occasional check-ins and booster sessions from the professional.

Schools may provide an excellent venue for delivering treatment, both by school personnel (for example, psychologists) and peer-support approaches. School space is frequently available at no cost after classes are over. The child, their peers and the psychologist are all present at the same location so there are no transportation costs and it is much less inconvenient to the parent than taking the child to a clinic for an appointment. There is potentially much less stigma for the child in attending a peer-support group at school than going to a psychiatric practitioner. To the extent that we target children with milder depressive symptoms or wish to provide very long-term therapy to prevent future episodes, convenience, economy and lack of stigma are all critical to success.

To the extent that treatment is provided in venues physically and emotionally close to the patient and family (for example, school or church), we may increase compliance with treatment and simultaneously train the organization in the recognition and management of other youth with MDD. Patients and families don't want to travel long distances for psychiatric treatment (Marcus et al., 1997a,b).

Individuals will all have their own responses to different treatments, their own issues with continuing treatment, and their own family and social environment, so it is essential to tailor the treatment to maximize the overall benefit to each individual.

Conclusions

Our understanding of the etiology and clinical course of mood and anxiety disorders in adults continues to be instrumental in the development of novel antidepressants. However, our understanding of the clinical course of mood and anxiety disorders in youth is not well established. Over the past decade we have acquired a considerable amount of knowledge about

the acute (short-term) treatment of non-refractory MDD in children and adolescents. Much of this knowledge was acquired through an understanding of the clinical course of MDD in adults and their response to treatment.

Both pharmacotherapeutic and psychotherapeutic treatments are effective in the short-term treatment and management of children and adolescents with MDD. However, despite the prevalence of MDD in youth it is under-recognized, under-diagnosed and under-treated. Ongoing studies provide opportunities to improve the recognition and diagnosis of MDD, and understand the clinical course of MDD and outcomes following treatment with pharmacotherapeutic agents, psychotherapy, or combination therapy in children and adolescents. In particular, understanding the long-term clinical consequences of this chronic, recurrent disorder will help to establish effective long-term treatment strategies for children and adolescents with MDD, thereby improving their chance of remission and of returning to normal social and work functioning.

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