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Diagnosis and Treatment of Dysthymia in Children and Adolescents

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Abstract

Dysthymic disorder is a chronic depressive condition occurring in 0.6–4.6% of children and 1.6–8.0% of adolescents. Although symptoms are less severe than those observed in major depression, childhood-onset dysthymic disorder is characterised by a persistent and long-term depressed or irritable mood (mean episode duration 3–4 years), a worse outcome than major depression and, frequently, comorbid disorders (in around 50% of patients). Long-lasting depressive symptoms seem responsible for long-term disabling consequences on social skill learning, psychosocial functioning and consequent professional life, probably contributing to a higher risk of relapse or development of major depression. Consistently, the first episode of major depression occurs 2–3 years after the onset of dysthymic disorder, suggesting that the latter is one of the gateways to recurrent mood disorders.

The primary aims of treatment for dysthymic disorder should be to resolve depressive symptoms, reduce the risk of developing other mood disorders over time and strengthen psychosocial functioning, especially in children and adolescents, in order to prevent the potentially serious sequelae of this disorder. As children with dysthymia often have multiple problems, interventions should involve multiple levels and measures: individual psychotherapy, family therapy/education and pharmacological treatment.

Psychotherapeutic techniques, such as cognitive-behaviour therapy and interpersonal therapy, have been found to be efficacious interventions in treating children and adolescents with mild to moderate depression in studies including patients with either dysthmia or double depression.

SSRIs are the first-line drug treatment for children and adolescents because of their safety, adverse effect profile and ease of use (the safety of paroxetine is currently under investigation). Several nonblind studies have shown the efficacy and good tolerability of SSRIs in children and adolescents with dysthymic disorder, but further research is needed to confirm their efficacy and that of newer antidepressants in the treatment of this disorder.

Regardless of whether psychotherapeutic or medical treatments are planned, according to clinical experience, psychoeducational interventions and psychosocial support should be provided to parents and other caregivers during the acute treatment phase to help manage the child's irritable mood and foster a therapeutic alliance and better compliance with treatment.

Unfortunately, no studies have focused on continuation treatment of paediatric dysthymic disorder. Given the chronicity, recurrence, psychosocial consequences and peculiar response pattern to treatment of dysthymic disorder, establishing

effective 'acute' and 'continuation' interventions in this group of patients should be a priority in mental health management.

1. Diagnosis

1.1 Clinical Phenomenology and Classification

Currently, according to DSM-IV,[1] children and adolescents can receive diagnoses of mood disorders with few modifications compared with the adult criteria. A diagnosis of dysthymic disorder is met when either depressed or irritable mood is evident (whereas adults must present with depressed mood) for most of the day, for more days than not and for a prolonged period (at least 1 year for children and 2 years for adults) in the absence of major depressive, manic or hypomanic episodes. Superimposed episodes of major depressive disorder may follow the first year of dysthymic disorder; in such cases, a DSM-IV diagnosis of double depression is appropriate. The additional DSM-IV criteria for early-onset and adult dysthymic disorder are identical and require two of the following six symptoms: (i) poor appetite or overeating; (ii) insomnia or hypersomnia; (iii) low energy or fatigue; (iv) low self-esteem; (v) poor concentration or difficulty making decisions; and (vi) feelings of hopelessness.

Compared with those with major depressive disorder, children with dysthymic disorder appear to have fewer melancholic symptoms and a significantly lower prevalence of guilt, morbid preoccupation and impaired concentration.[2] Reduced appetite is virtually absent in children with dysthymic disorder, and few experience hyposomnia and fatigue; disobedient behaviour, probably as a feature of irritable mood, is the most prevalent sign.[2]

The mean age of onset of dysthymic disorder ranges between 10.1 ± 4.9 and 13.8 ± 3.1 years, as reported in different studies.[3,4] The age of onset of dysthymic disorder is significantly lower than that of major depressive disorder, and the presence of dysthymic disorder does not influence the age at which the first episode of major depressive disorder develops.[3,4]

Dysthymic disorder in children occurs at the same rate in boys and girls, whereas the female-male ratio for dysthymia in adolescents is approximately 2 : 1, paralleling the ratio reported in adults.[5]

1.2 Comorbidity

Comorbidity is an evident clinical phenomenon in child and adolescent dysthymic disorder. Estimates of lifetime comorbid psychiatric disorders and pathological behaviours in children and adolescents indicate that dysthymic disorder is often associated – either at onset or during the natural course of the illness – with numerous conditions, such as anxiety disorders, behavioural problems or substance abuse, which may complicate the clinical picture or response to treatment.[6] Estimates from a community-based sample of adolescents with dysthymia show that around 50% of them have other pre-existing psychiatric disorders, including anxiety (40%), conduct disorders (30%), attention-deficit hyperactivity disorder (ADHD) [24%] and enuresis or encopresis (15%), with 15% of them having two or more comorbid disorders.[2]

As for major depressive disorder, comorbid conditions seem to be a predictor of additional treatment in the acute phase and of a worse treatment outcome at follow-up.[7-9]

1.3 Natural History and Clinical Outcome

Evidence from longitudinal studies shows that early-onset dysthymic disorder is better conceptualised as a long-lasting condition with a heightened

risk for relapse and later recurrent mood disorder than as a disorder with mild symptomatology and good outcome. Consistently, major depressive, manic or hypomanic episodes occur with a frequency significantly higher than chance at some point during the natural course of the illness, with a median interval of 2–3 years between dysthymic disorder onset and the first episode of major depressive disorder.[2,4,10]

In a naturalistic follow-up study of a cohort of outpatients with early-onset dysthymic disorder (before the age of 21 years), an estimated risk of 76.9% and 5.8% was reported for superimposed depressive and manic episodes, respectively.[4] Because 77.9% of the subjects with dysthymic disorder had already experienced a superimposed major depressive disorder by the beginning of the study, 94.2% of the subjects had at least one lifetime major depressive disorder by the end of the follow-up. These data suggest that almost all individuals with dysthymic disorder will eventually experience major depressive disorder at some point in their lives.[4]

Patients with dysthymia experience mild symptoms but long episodes, whereas major depressive disorder shows exactly the opposite pattern. Estimates of duration of dysthymia vary across different studies from 2.5 to 3.4 years in clinically referred and community-based youths.[3,7]

Once patients recover from an episode of dysthymic disorder, they are at high risk of relapse for the same disorder, the estimated relapse rate being 45.2%.[4] It has been estimated that, given a 5-year observation span, children and adolescents with a diagnosis of dysthymic disorder show symptoms of mood disorder for approximately 70% of the time for at least three reasons: (i) they develop recurrent mood disorder; (ii) they relapse into subsequent dysthymic episodes; and (iii) the duration of illness is long. Although dysthymic disorder often presents with mild symptoms, from a longitudinal perspective it is more severe than major depressive disorder and is a significant public health problem. Taken together, these data highlight how important it is to correctly identify dysthymic disorder among children and adolescents. The development of effective strategies for long-term treatment of dysthymic disorder is crucial for shortening the symptomatic phase of the episode, reducing the risks of recurrent affective illnesses (major depressive disorder and bipolar disorder) and relapse prevention.

1.3.1 Double Depression

The superimposition of major depressive disorder on the course of dysthymic disorder gives rise to the picture of 'double depression'[11] that has now been incorporated into the DSM-IV as a common basic course pattern of depressive illness. The rate of double depression varies across samples: two studies[2,12] reported a high rate (nearly 70%), while others reported moderate[6] (around 30%) to low[13] (17%) rates among children.

There could be at least two explanations for the co-existence of the two disorders: (i) major depression, dysthymia and their overlap might be different manifestations of the same disorder or different steps on a continuum of severity; and (ii) major depressive disorder and dysthymic disorder are two distinct disorders, and higher than chance co-occurrence might be a result of either environmental or genetic shared liability.

Youths with both major depressive disorder and dysthymic disorder have been found to have more severe and longer depressive episodes, a higher rate of comorbid disorders, more suicidality and higher social impairment than youths with major depressive disorder or dysthymic disorder alone.[2] Whatever the nature of the relationship, it is clear that youths with double depression do recover from episodes of major depressive disorder, but most of them quickly relapse into a new episode, with an estimated 84.4% rate of second relapse.[4]

1.3.2 Suicidal Behaviour

The clinical presentation of suicidal behaviour includes a wide range of psychopathological experiences with increasing degrees of severity, such as persistent suicidal ideation, suicidal threats, suicidal attempts and successfully completed suicide. Developmental factors influence the clinical manifestation of suicidal behaviours, most evident in the epidemiology of suicidal behaviour: completed suicide is significantly rare before puberty and becomes increasingly frequent through adolescence, reaching a peak between the ages of 19 and 23 years. Completed suicide is much more common among boys than girls, while suicide attempts are more common with girls.[14]

Dysthymic disorder represents a common risk for suicide attempts, with rates varying between 9.5% and 19% in the adolescent population.[4,6] The presence of comorbid conduct and/or substance use disorders further increases the risk of suicide attempts,[15] while superimposed major depressive disorder does not.[4] General recognised risk factors for suicide that increase the likelihood of a suicide attempt or a suicide in the context of a dysthymic disorder, regardless of the associated psychopathology, include a history of physical and sexual abuse, positive family history for suicidal behaviours and a previous suicide attempt.[16-18]

1.3.3 Functional Impairment

Psychosocial disturbances are common in dysthymic disorder, but it is unclear whether they represent a precursor, a state condition or a long-term consequence of the disorder. In a community-based sample of adolescents, lifetime dysthymic disorder was more frequently associated with psychosocial difficulties at onset (i.e. no sports activities, poor relationships with siblings, mother and father, and problems with relatives).[6] In the few studies that have investigated psychosocial functioning during the symptomatic period, children and adolescents with dysthymia were found to frequently experience impairments in relationships with peers,[4] which in turn is a risk factor for lower functioning, especially during such a critical period of development. Psychosocial functioning is negatively correlated with the duration of dysthymic disorder and worsens with increasing severity of diagnosis and presence of comorbidity.[19] Data are controversial regarding the impact of dysthymic disorder on academic performance.[4,6]

Few studies have focused on the psychosocial consequences of adolescent dysthymic disorder; those that did found that adolescents with long-lasting dysthymic disorder or double depression have a poorer outcome and more limited social interaction when they become adults compared with subjects with a history of major depressive disorder only or nonaffective disorder in adolescence.[13,20,21] These data suggest that adolescents with dysthymic disorder continue to experience significant difficulties in psychosocial functioning even after recovery, with a worse outcome than adolescents with past major depressive disorder. This is probably a result of the negative impact of the shorter disorder-free periods with dysthymic disorder than with major depressive disorder on the overall developmental process.[4]

2. Epidemiology

2.1 Prevalence

Epidemiological studies have reported point prevalence rates for dysthymic disorder ranging between 1.6% and 8.0% in adolescents and 0.6% and 4.6% in children, and the 6-month prevalence rate for double depression is 9.9%.[22-26] In a sample of high-school students aged 14–18 years, Lewinsohn et al.[22] reported a 1-year first incidence of dysthymia of 0.13% and 0.0% for girls and boys, respectively. An epidemiological study of adolescents aged 11–16 years showed a 3.4% weighted 1-year incidence of dysthymic disorder, which was found

by examining those individuals with no disorder at baseline.[4]

2.2 Risk Factors

Numerous factors are potential candidates to differentially influence the onset and natural course of dysthymia: demographic factors (age, sex, socioeconomic status), concurrent psychopathology (pre-existing diagnosis), familial factors (parental psychopathology, high genetic loading for mood disorders) and psychosocial factors (poor support, stressful life events, poor maternal functioning). Dysthymic disorder aggregates specifically in families of patients with the same disorder, and relatives of patients with dysthymic disorder and those with major depressive disorder show higher rates of major depressive disorder compared with the relatives of healthy control individuals, thus suggesting that dysthymic disorder and major depressive disorder show strong familial relationships, although they may have distinct patterns of familial transmission.[27]

Abnormal family interactions might intuitively increase the risk of developing dysthymic disorder, even though the exact mechanism underlying this relationship is not known and could be a nonspecific risk factor for child psychopathology. However, dysthymic disorder was associated with high levels of adverse early home environments in childhood and parental psychopathology, even though no distinction could be made clearly between genetic and environmental effects.[28,29] Among life events, physical abuse and illness or death of a close relative seem to be specifically related to the onset of dysthymic disorder during adolescence.[6,30]

3. Treatment

The primary aim of treatment of dysthymic disorder is to resolve depressive symptoms (i.e. remission). This would be especially desirable in individuals at an early developmental age, because it could prevent the high risk of their developing other mood disorders over time[2,4,10] and reduce the long-term disabling consequences on their social skills learning and consequent professional lives. Intervening in the disorder shortly after its onset may offer a window of opportunity to prevent its potentially serious sequelae (academic failure, substance abuse, suicide attempts and suicide).[31]

Despite the great number of children and adolescents with dysthymic disorder, very few controlled studies have been carried out on the psychological and medical treatment of youth with dysthymic disorder or comorbid dysthymic disorder and major depressive disorder. In clinical practice, the same interventions for children and adolescents with major depressive disorder are usually recommended for the treatment of paediatric dysthymia.[32] Nevertheless the peculiar aspects of this disorder should be taken into account when developing a specific treatment plan. Improvement of depressive symptoms may not necessarily parallel functional improvement (which is particularly impaired).[4] On the other hand, as a result of its chronicity, dysthymic disorder may require longer treatment and more frequent sessions than other depressive disorders,[33] which imply greater economic impact on either the families of patients or healthcare systems. So far, no study has been able to define the optimal duration of an effective treatment for children and adolescents with dysthymic disorder.

Furthermore, few studies have focused on the treatment outcome of patients with dysthymic disorder and comorbid conditions. As for major depressive disorder, comorbid conditions are likely to worsen the treatment outcome. For instance, Kovacs et al.[7] found that externalising disorders affect the duration of dysthymia and suggested implementing interventions for behaviour problems to shorten this type of depression. Brent et al.[8] found that subsyndromal depressive symptoms, behavioural problems and family conflicts at the end of acute treatment predicts the need for further treatment at follow-up.

Finally, Brent et al.[34] found that comorbid anxiety among depressed children (major depressive disorder and dysthymic disorder) was associated with poorer treatment response.

3.1 General Treatment Approach

A comprehensive diagnostic evaluation of children and adolescents with dysthymia requires separate interviews with the patient and the parents, since children are often more aware of internalising symptoms, whereas their parents are more aware of behavioural problems.[35] Assessment should include a careful evaluation of psychosocial stressors, family functioning, school environment and the individual's coping ability.[36]

The frequently comorbid diagnoses[4] (about 50% of patients have comorbid diagnoses) should be addressed concurrently in the treatment of a child with dysthymia.

Treatment should be individualised and based on needs as well as resources and assessment of stressors. As children with dysthymia often have multiple problems, interventions should occur at multiple levels, including individual psychotherapy, family therapy/education and pharmacological treatment. Psychoeducational interventions and psychosocial support are an essential component of an individualised treatment plan, regardless of whether specific psychotherapy or medication is used.[36]

3.2 Assessment Procedures and Measures

Severity of symptoms and global functioning should be evaluated before treatment, at clinical re-evaluation and at follow-up. Severity of depressive symptoms can be assessed by one of the available depression scales, such as the self-administered Children's Depression Inventory (CDI)[37] or the observer rated Hamilton Depression Rating Scale (HAM-D).[38] Impairment in global functioning can be evaluated using scales such as the Children Global Assessment Scale (CGAS)[39] or Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA).[40]

4. Psychological Treatment

The general aims of psychological treatments in childhood and adolescence are "to modify maladaptive personality organisation that may determine long-term change in mood",[41] to enhance behavioural, cognitive and emotional management skills to cope with present and future stressful life events, and to obtain full remission of symptoms as well as prevent recurrence.

Psychological treatment is the only intervention possible when a family refuses pharmacological medication or when the patient is not responsive to antidepressants.[42]

Response to psychotherapy is related to several factors, including "age at onset, severity of depression, presence of comorbid psychiatric disorder, degree of support, parental psychopathology, family conflict, exposure to stressful life events, socioeconomic status, quality of treatment, the therapist's expertise and motivation of both patient and therapist",[32] as well as the family's understanding of depressed mood and their ways of managing it. All these aspects should be taken into account when devising treatment plans, since they can influence the initiation, maintenance and recurrence of depression. For instance, Kovacs et al.[7] found that the duration of dysthymic disorder in children and adolescents was predicted by comorbid externalising disorders (conduct, oppositional, attention-deficit) and suggested addressing behavioural problems to shorten depression, since depressive symptoms may be a way of coping with the negative social reactions that conduct disturbances elicit.

4.1 Psychoeducational Interventions

On the basis of clinical experience and in line with the Practice Parameters for Assessment and Treatment of Children and Adolescents with De-

pressive Disorders,[32,43,44] psychoeducational interventions should always be provided to the child, his/her parents and other caregivers during the acute treatment phase regardless of whether psychological treatments or medication are used. The aims of psychoeducational interventions are to inform the child, the family and the school about symptoms, their consequences, prognosis, treatment duration and adverse effects of medication as well as to provide educational guidelines in order to help the child cope with depressed mood and foster a better compliance with treatment.

The child is encouraged to divert from the tendency to ruminate on 'bad' feelings and to spend as much of the day as possible functioning normally, regardless of how he/she may feel inside by reducing his/her time alone, and by attending school and continuing weekly activities.[36]

Parents and family members need to be informed about clinical aspects and biological/psychological determinants of depression and instructed about the child's need for reassurance and support, rather than punishment for unacceptable behaviour. Education of all family members is essential because the symptoms of depression (lack of interest, fatigue, isolation and irritability) may affect the response of each member of the family to the patient and increase their emotional involvement, "causing more stress, guilty or angry feelings for the patients to cope with".[32] Furthermore, these instructions decrease self-blaming ("I'm a bad parent") and the tendency to blame the youth ("He is just lazy"). Finally, the family should be involved in the development of treatment plans and the identification of areas for change.[36]

There is evidence that depressed youth often do not seek treatment,[45] and clinical experience has shown that withdrawal from treatment greatly diminishes with the addition of an educational component. The school setting should be adapted as much as possible to reduce stress, for instance by limiting the number of school demands and focusing less on deficits when the dysthymic disorder is diagnosed with a comorbid learning disability.

4.2 Supportive Treatment

The goals of supportive interventions are to establish, maintain and build rapport and provide support, as well as improve self-concept by aiding the patients in the identification and expression of feelings through reflective listening and empathy. In this type of treatment, the therapists refrain from giving advice, setting limits and teaching skills.

Although individual supportive treatment was not found to be as effective as other more structured therapies such as cognitive behavioural therapy (CBT),[43] supportive group treatment was found to be more helpful than a problem-solving group in the reduction of depressive symptoms in adolescents with either dysthymia or major depressive disorder.[46]

4.3 Cognitive Behavioural Psychotherapy

Controlled studies on the psychotherapy of depression are mostly within the cognitive-behavioural framework.[47] CBT is generally a time-limited intervention, primarily targeting cognitive, behavioural patterns and affecting management skills;[48] it is delivered in either individual or group formats. The duration of CBT in studies on child and adolescent depression ranges from 5 to 16 weeks.[48] The theoretical assumption of this approach is that automatic, irrational thoughts and maladaptive coping behaviours are responsible for depressive symptoms and mood[49] and that their replacement with more adaptive self-statements and coping skills will reduce depressive symptoms. The interventions are based on various techniques to help patients self-monitor, set goals, identify and change distorted cognitions, increase their social problem-solving skills and engage in more pleasant activities as well

as manage affects through relaxation and impulse control techniques.

No studies of psychological treatments in youth have focused on dysthymic disorder only. Most studies include subjects with a diagnosis of major depressive disorder or dysthymic disorder or both, without differentiating the effects[50-53] and thus making it difficult to identify differential response rates according to clinical conditions.[47] However, several studies have tested CBT on adults with dysthymic disorder only,[54] showing response rates at the end of treatment ranging from 20% to 67% after 4 months of CBT.[55,56] The rates of recurrence or relapse at follow-up after treatment are not clear for children and adolescents with dysthymic disorder since no distinction is made from patients with major depressive disorder. However, "all clinical studies of CBT on depressed children and adolescents have found a high rate of relapse on follow-up, suggesting the need for continuation treatment".[32]

4.4 Interpersonal Therapy

Like CBT, interpersonal therapy (IPT) is time limited and manual based; "the therapist helps the patients recognise links between mood and current interpersonal experiences, focusing on different problem areas"[54] such as grief, interpersonal roles, disputes, role transitions and interpersonal difficulties. Its efficacy is proven for the acute treatment of adolescents with major depressive disorder[57-59] and for adult patients with dysthymic disorder.[60] In a study by Rossellò and Bernal,[61] adolescents with major depressive disorder or major depressive disorder with dysthymia were randomly assigned to CBT, IPT or a wait-list condition. IPT and CBT reduced overall depressive symptoms when compared with the wait-list condition. Youth treated with IPT improved more in self-esteem and social adaptation compared with the wait-list condition.

4.5 Family Therapy

Family therapy is recommended for youth because of the frequent association between depressive symptoms and family dysfunction,[62] which can reflect both environmental mechanisms and genetic factors. High parental criticism,[63] family discord[64] and poor parent-child communication[65] are often observed in families of depressed children and adolescents. Durbin et al.[66] found that familial psychopathology, including the patient's poor relationship with their own parents and high familial loading for drug abuse and personality disorders, is the most effective predictive variable of outcome in dysthymic disorder, thus stressing the need for family involvement in treatment plans.

Most therapists working with children and adolescents involve parents in the treatment at some point, but systematic clinical guidelines on how to involve them are needed. Only a few controlled studies have been carried out on the effect of family involvement on treatment of depressed children and adolescents, none of them showing significant effects compared with the control conditions represented by CBT and supportive therapy only.[43,50]

4.6 Psychodynamic Psychotherapy

Psychodynamic therapy of depression has been reported as being effective by some but not all clinicians. Some positive case reports are available,[67] but it has been argued that gathering strong evidence in favour of or against the efficacy of this approach through controlled clinical studies would be time consuming and expensive. Additional research with standardised measures and control groups is surely needed. Psychodynamic psychotherapy may help youth understand themselves, identify feelings, improve self-esteem, change maladaptive patterns of behaviour, interact more positively with others and cope with ongoing and past conflicts.[67]

4.7 Prevention Programmes

Prevention programmes are implemented to prevent dysthymia (primary prevention) and recurrence after remission of symptoms.

Programmes on primary prevention are of two types: universal and targeted. Universal programmes "involve all individuals in a population regardless of their level of risk"; they consist of educational group sessions aiming to develop social skills with a view to develop strengths against depression.[68] This type of intervention did not show significant benefits compared with a no-intervention condition.[68] Targeted prevention programmes target a population of children and adolescents with high levels of risk for depressive disorders. These at-risk individuals are selected on the basis of high scores on self- or parent-reports and/or have a family history of depression or report parental conflict. Again, programmes focus on social skills training and sometimes education of parents and teachers about depressive symptoms. Encouraging results were achieved in some studies with these high-risk populations, leading to a significant reduction in depressive symptoms at follow-up.[69,70]

A further case for the implementation of prevention programmes may be seen in the findings of relatively poor treatment response and relapse rate at follow-up in childhood and adolescence dysthymia.[46,52] There is no strong evidence yet for the preventive effects of psychological treatment against recurrence, but available results suggest that booster sessions should be included in treatment programmes to limit the risk of relapse and accelerate recovery among patients who were still depressed at the end of the treatment.[53]

5. Pharmacological Treatment

The decision on whether or not to treat a child with pharmacotherapy should ideally be based on data about the efficacy of a given drug in controlled studies for a specific disorder in a specific age group. There are no data from controlled trials in paediatric dysthymia. Only a few open studies have evaluated the therapeutic effect of SSRIs (fluoxetine, paroxetine, fluvoxamine, citalopram and sertraline) in children and adolescents with dysthymia. Nevertheless, the use of antidepressants in the treatment of child and adolescent dysthymia appears reasonable in light of the significant impairment associated with this disorder, the multiple lines of evidence suggesting continuity from child and adolescent dysthymia to adult mood disorders and the well established efficacy of antidepressants (tricyclic antidepressants [TCAs], monoamine oxidase inhibitors [MAOIs], SSRIs and serotonin/noradrenaline (norepinephrine) reuptake inhibitors [SNRIs])[71-73] in the treatment of adult chronic depression.

Considering that the majority of the studies in childhood depression have focused on major depressive disorder and only a few on dysthymia or both major depressive disorder and dysthymic disorder, general principles for the pharmacological treatment of paediatric major depressive disorder may also be applied to the treatment of dysthymia with some specific caveats as discussed in the next sections.

5.1 Indications

The initial decision is whether or not to start a trial of antidepressants. Unlike major depression, where the severity of depressive symptomatology and recurrence[36,74] are the main criteria for medication, in dysthymic disorder, criteria could be the severity of psychosocial impairment in family and peer functioning or school performance and the co-occurrence of a major depressive episode (double depression) [table I]. Functional impairment appears to be greater for double depression than for pure episodic major depression.[75]

Prior to the initiation of medication, the impairment in global functioning and the severity of symp-

Table I. Indications for initiating medication in childhood dysthymia (reproduced from Emslie and Mayes,[36] with permission)

Severity of psychosocial impairment in family and peer functioning or school performance
Other family member's response
'Double depression'
Comorbidity
No response to psychotherapy
Convenience for family
Psychosocial stressors

toms should be measured using one of the available scales, as discussed in section 3.2. There is no need for baseline laboratory testing prior to initiating treatment with SSRIs or SNRIs except for a review of the last menstrual period and a pregnancy test in adolescent girls if indicated;[76] before starting one of the TCAs, a baseline ECG, resting blood pressure and heart rate (supine, sitting and standing) as well as bodyweight should be recorded. No other tests are usually indicated in a healthy child before starting antidepressant therapy.[77]

The decision to initiate drug treatment must actively involve adequately informed parents with the child's assent. It is vital to educate parents and patients about adverse effects and toxicity.[77]

5.2 Pharmacological Agents

5.2.1 SSRIs

SSRIs are the first-line treatment for child and adolescent depression because of their safety, adverse effect profile, ease of use and efficacy.[42,77,78] SSRIs have been shown to selectively block the presynaptic neuronal reuptake of serotonin with little or no affinity for adrenergic, cholinergic or histaminic receptors.[79] Currently available SSRIs are fluoxetine, paroxetine, sertraline, citalopram and fluvoxamine. At present, fluoxetine is the only drug officially approved by the US FDA to treat major depressive disorder in children and adolescents 7–17 years of age. Several nonblinded studies have shown the efficacy and good tolerability profile of SSRIs in children and adolescents with dysthymic disorder.

Fluoxetine

Waslick et al.[80] used fluoxetine (20mg daily) to treat 19 paediatric patients with dysthymic disorder (n = 7) or double depression (n = 12) whose symptoms had not responded to brief (4 weeks) psychosocial treatment alone. After 8 weeks of treatment with fluoxetine, 73% of patients no longer met the criteria for dysthymic disorder or major depressive disorder (67% and 78%, respectively). It was noted that treatment was associated with significant improvement in depressive symptoms, but the overall improvement in terms of functioning was rather modest. This could certainly be explained in terms of residual impairment in school, interpersonal or family functioning that could be expected after the patients had been depressed for a significant part of their early developmental years.

Fluvoxamine

Rabe-Jablonska[81] studied the therapeutic effect of fluvoxamine (150–200mg daily) in 21 adolescents with dysthymia in a 26-week open-label study. Good clinical response as determined by a 50% decrease in HAM-D baseline scores was noted in 56% of patients at 8 weeks. Relapse of dysthymic symptoms occurred in 34% of patients after 26 weeks of receiving medication. Fluvoxamine was well tolerated in 76.2% of adolescents; poor tolerability resulted in a discontinuation rate of 14.2%. (The reported response rate of 34% at 26 weeks is difficult to interpret, as the author reported that 3 of the 18 patients had discontinued fluvoxamine sometime after week 8).

Paroxetine

Nobile et al.[82] examined the efficacy of paroxetine in the treatment of seven children and adolescents with dysthymic disorder over a period of 3 months. Seventy-one percent of patients had a satisfactory response, defined as both a ≥50% improve-

ment from baseline HAM-D score and a Clinical Global Impression Improvement (CGI-I) score of much or very much improved. Clinical evaluation of responders at 6 months after the beginning of therapy suggested stability of improvement over time. The mean dosage of 20.12 mg/day was similar to the dosage of paroxetine prescribed for children with major depression,[83] and the pattern and incidence of adverse effects were similar to those of other SSRIs[79] in depressed children and adolescents.

The efficacy of 8 weeks' treatment with paroxetine was also assessed in a retrospective study of seven adolescents with dysthymia (from a total sample of 25 depressed adolescents).[73] Seventy-one percent of patients treated with paroxetine (20–40mg daily), administered either as monotherapy or with benzodiazepines, showed a satisfactory response (three total remissions and two improvements with residual symptoms). Adverse effects in the whole group did not differ from those expected for SSRIs in adults and adolescents.

The safety of paroxetine is currently under investigation (see section 5.5) and, as a result, use of the drug in patients <18 years of age cannot currently be recommended.

Sertraline

Nixon et al.[84] looked at the effects of sertraline (50–200mg daily) in adolescent major depressive disorder (n = 13) and dysthymic disorder (n = 8) in a 6-month open trial. The major depressive disorder group showed maximal clinical response at weeks 12 (76.9%) and 20 (76.9%). The response rate was maintained at week 24, with all six patients who completed the study responding to treatment. The dysthymic disorder group achieved maximal response at week 6 (85.7%); response rates in this group did not remain elevated over time, with only two of three completers (66.7%) responding to treatment at week 24. Overall, the dysthymic disorder group displayed a higher incidence of adverse effects, notably nausea and headache, than the major depressive disorder group. The mean average daily dose was only slightly higher in the dysthymic disorder group (140 vs 125mg).

Citalopram

Bostic et al.[85] assessed the effectiveness of citalopram in 21 adolescents with depressive disorder (major depressive disorder, n = 14; bipolar disorder, n = 4; dysthymic disorder, n = 3) treated naturalistically in a community mental health centre over a 1-year interval. Seventy-six percent of the whole group were much to very much improved on the CGI-I scale, while all patients with dysthymia were very much improved. The median dosage of citalopram was 25 mg/day; mild adverse effects, including headaches, dizziness, nausea, sedation, agitation and sweating, were reported by 33% of patients.

5.2.2 Tricyclic Antidepressants

Several well designed trials of treatment with TCAs in depressed children and adolescents have failed to demonstrate the effectiveness of the drugs compared with placebo.[77,86] No data are available regarding the use of TCAs for the treatment of children and adolescents with dysthymia. Given their frequent adverse effects, lethality in overdose and potentially serious cardiotoxicity, TCAs should not be considered as first-choice medication in dysthymic disorder, although some patients may respond positively.

5.2.3 Other Antidepressants

Very few studies exist on the use of other antidepressants (e.g. bupropion, venlafaxine, nefazodone and MAOIs) in the treatment of depressed children and adolescents,[77] and no study has been carried out on children and adolescents with pure dysthymia.

A recent controlled double-blind study comparing venlafaxine and placebo in a sample of children and adolescents with depression (n = 30) using small doses of venlafaxine (up to 75mg daily) showed no differences in outcome or adverse effects between

venlafaxine and placebo.[87] Venlafaxine has been found to be more efficacious than paroxetine in treating adult dysthymic disorder,[73] but so far this has not been shown in children and adolescents.

In two open naturalistic trials,[88,89] nefazodone was well tolerated and associated with a significant reduction in depressive symptoms in children and adolescents with major depressive disorder.

Bupropion is a novel antidepressant with agonistic effects on the noradrenergic system and, to a lesser extent, the dopaminergic system,[90] each being potentially relevant for the treatment of depression and ADHD. Arredondo[91] evaluated its efficacy in adolescent major depressive disorder and found a significant improvement in eight of ten adolescent inpatients.

Daviss et al.[92] evaluated a sustained release (SR) formulation of bupropion in 24 adolescents with ADHD and major depressive disorder (n = 2) or dysthymic disorder (n = 7) or both (n = 15). The study was open-label in design and used doses flexibly titrated up to 3 mg/kg twice daily, after a single-blind placebo lead-in. The authors noted final global response rates of 88% for depressive disorders and 63% for ADHD, with 58% of patients appraised as simultaneous responders for both disorder groups. Bupropion SR was generally well tolerated, although various adverse effects were reported more frequently during active medication than during the patients' placebo lead-in phase, including rashes, irritability, tremors and tics; no patients discontinued the medication because of adverse effects.

5.3 Acute-Phase Medication

Although further controlled studies are needed on larger samples, the results reported in section 5.2.1 suggest that SSRIs should be considered first-line agents in the acute-phase treatment (i.e. the first 8–12 weeks of treatment) of dysthymic disorder in children (the UK MHRA and US FDA have advised that paroxetine should not be prescribed for children and adolescents; see section 5.5). Starting dosages should be lower than those used in adults and slowly increased to target dosages[42,76,77,79,93] as specified in table II. In our clinical experience, this reduces the incidence of adverse effects, particularly sleep and gastrointestinal disturbances, thus enhancing the collaboration of patients and their families with treatment.

Patients should be treated with adequate and tolerable doses for at least 8 weeks to assess treatment response. A regular review of symptoms, global functioning and adverse effects using one of the available scales with the child and the parents is recommended; it is believed that close monitoring results in more favourable outcome (as a result of increased patient adherence). In addition, more frequent contact enhances the engagement of the child and family in treatment and provides additional opportunities for education.[74,94]

If at 4 weeks there is minimal improvement, increasing the dose could be an option. On the other hand, if an aggravation of symptoms or severe adverse effects are observed, it is advisable to consider changing medication (see section 5.4). For patients showing minimal or no response, the total trial should not exceed 4–8 weeks. For patients with a partial response, the trial may last up to 12 weeks.[42,74]

5.4 Partial Response and Nonresponse

Patients with symptoms not responding to adequate treatment should be assessed for the quality of the therapeutic relationship, adverse effects, dose,

Table II. Approximate suggested dosages for antidepressants in children and adolescents with dysthymia[42,76,77,79,93]

Medication	Initial dosage (mg/day)	Paediatric dosage range (mg/day)
Fluoxetine	5	10–30
Sertraline	25	50–200
Fluvoxamine	25–50	50–200
Citalopram	10	10–30
Venlafaxine	12.5–25	37.5–75

duration and, particularly, adherence.[32] In addition, the recommendations of the Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder[74] should also be considered for patients with dysthymic disorder: (i) reassess the diagnosis for previously unrecognised comorbid conditions; (ii) consider the possibility of an unrecognised general medical condition; (iii) re-evaluate the patient's exposure to negative psychosocial stressors; (iv) assess the quality of treatment; and (v) re-evaluate family functioning or look for psychopathology in other family members.

For patients with symptoms not responding to their initial medication, three strategies can be pursued: optimisation, substituting with another drug, and augmentation or combining antidepressants.[42,74] Optimisation involves increasing the dosage gradually, adverse effects permitting, and maintaining the increased dosage for 6–8 weeks. The second strategy (substitution) is based on the fact that a lack of response to one SSRI does not necessarily predict a lack of response to another agent of the same class. In the third, lithium augmentation has been described in adolescent depression.[95,96] Only a few noncontrolled data are available on augmentation treatment in adult dysthymia,[97,98] and no data are available for children and adolescents with dysthymia.

5.5 Adverse Effects

Available data indicate that SSRIs are well tolerated in the short term, but further research is needed to provide the necessary information on long-term effects in children and adolescents.

In June 2003, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) advised that paroxetine should not be prescribed for children and adolescents.[99] It did so on the recommendation of an independent expert working group commissioned by the Committee on Safety of Medicines (CSM). The advice is based on studies showing that there are higher rates of suicidal thoughts and behaviour in the patients who took paroxetine (25 of 738; 3.4%) compared with those who took placebo (8 of 647; 1.2%). There was no case of an actual suicide in the patients in these studies. Nine studies into the drug had been conducted, but the result of only one was 'in the public domain', and researchers and clinicians cannot access the data on which the MHRA recommendations are based. GlaxoSmithKline, the manufacturer of paroxetine, noted that conclusions drawn from their data differ to those drawn by the MHRA.

The US FDA is currently reviewing these data. Although the US FDA has not completed its evaluation, it is recommending that paroxetine not be used in children and adolescents for the treatment of major depressive disorder until further evidence from the scientific community is available and in the meantime suggests the use of other approved treatment options available for depression in children.

The most common adverse effects seen with SSRIs are gastrointestinal disturbances, headache, dizziness and initial insomnia.[77,79] Some of these disturbances (in particular, gastrointestinal disorders) have been reported to be more frequent in patients with dysthymia.[84] On the other hand, somatic complaints are common symptoms of paediatric dysthymia. Gastrointestinal adverse effects may be eased by a low starting dose or by taking medication with food.[76,79]

Another important adverse effect of all antidepressants is induction of mania or hypomania. This is not to be confused with akathisia and restlessness, which can be adverse effects of the rapid induction of SSRI treatment. In about 13%[2] of patients, dysthymia will evolve into a bipolar disorder (and the patients will probably develop manic symptoms when treated with SSRIs or other antidepressants). For the majority of patients, manic symptoms subside quickly after discontinuation of antidepressants.

5.6 Continuation Treatment

All recommendations for continuation-phase treatment for children and adolescents with dysthymia are based on adult data[100-103] and studies of child and adolescent major depressive disorder.[36,42,74,77] However, evidence suggests that the mean duration of dysthymia is up to 3 years and that there is an estimated 76.9% risk[4] of developing a superimposed major depressive episode. Therefore, continuation of medication for 6–9 months is recommended after symptom remission at the full therapeutic dose used in the acute phase.

Pharmacological data from the only two 6-month studies[81,84] reported in the literature suggest that children and adolescents with dysthymia have a different response pattern from those with major depressive disorder: patients with dysthymic disorder did not maintain acute-phase treatment response rates like those with major depressive disorder, with a 34% relapse rate. Another study on paediatric dysthymia[80] suggests that during the acute phase only, depressive symptoms improved, while the overall improvement in terms of functioning is rather modest. As mentioned in section 5.2.1, this could be explained by residual functional impairment, which could determine relapse or recurrence of the illness.[72,103,104]

The authors believe that, during the continuation phase, the introduction of CBT or 'booster' sessions to consolidate the skills learned in the acute phase could be the best way to prevent relapse and long-term sequelae.[42,53,103] It could be hypothesised that remission of depressive symptoms may enable the child to gradually return to higher levels of functioning and a normal developmental trajectory. The peculiar response pattern of dysthymic disorder in acute- and continuation-phase treatment highlights the importance of investigating both acute and continuation phases in treatment outcome studies of this disorder. Long-term maintenance pharmacotherapy may be considered for patients who have had two or more major depressive episodes in comorbidity with dysthymia or persistent functional impairment.

Antidepressants should be discontinued gradually over 6 weeks under close supervision and planned with patients and parents to avoid discontinuation syndromes and relapse.[105] As a relapse of dysthymic symptoms or a new major depressive episode[4] is likely to occur, the patient should be seen every 2–4 months; patients and their parents should be taught to monitor for recurrence of depressive symptoms.

5.7 Treatment of Comorbid Conditions

In addition to the treatment of depressive symptoms, it is crucial to treat the comorbid conditions that frequently accompany dysthymic disorder. As mentioned in section 1.2, comorbid conditions may influence the initiation, maintenance and recurrence of dysthymic disorder, with externalising, disruptive disorders predicting a worse outcome. Specific treatment guidelines for each of the comorbid disorders should be considered. If possible, a clinician should choose the medication that optimises response for dysthymia and the comorbid disorder. For example, SSRIs may help relieve both anxiety and dysthymia in children and adolescents.[106] Bupropion SR appears to be useful for treating ADHD that is comorbid with dysthymia and major depression in children and adolescents.[92] Nevertheless, at times it may be necessary to use two medications to treat two concomitant conditions (i.e. SSRIs and stimulants for comorbid dysthymic disorder and ADHD).

6. Conclusion

All cases of dysthymic disorder require careful evaluation of depressive symptoms, comorbidity, chronicity, functional impairment, psychosocial stressors, family functioning, school environment and the individual's coping ability. The treatment plan should be individualised and, possibly, should involve multiple levels and measures: individual

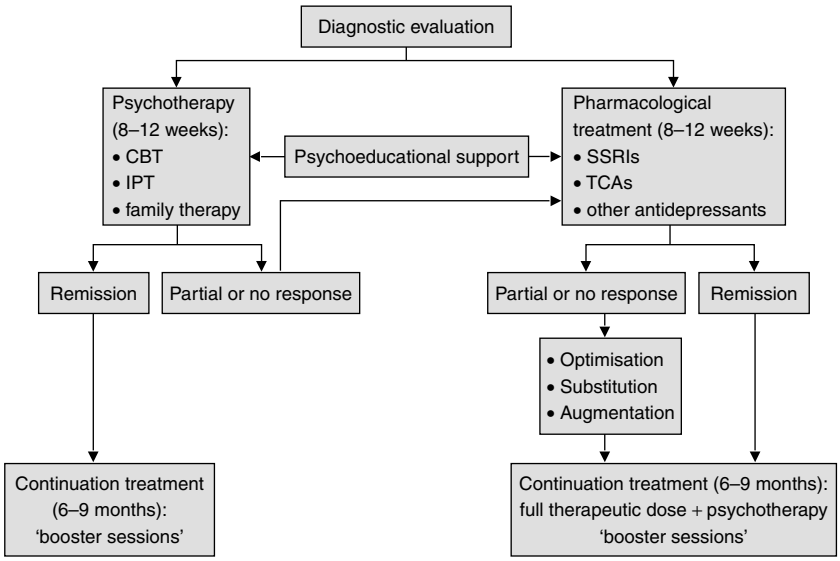

Fig. 1. Hypothetical integrated approach to the management of dysthymic disorder in children and adolescents. **CBT** = cognitive behavioural therapy; **IPT** = interpersonal therapy; **TCAs** = tricyclic antidepressants.

psychotherapy, family therapy/education and, eventually, pharmacological treatment (figure 1).

Psychotherapies have been shown to be efficacious for the treatment of children and adolescents with mild to moderate depression (including dysthymic disorder and double depression). Thus, we would recommend initially an 8- to 12-week trial of psychotherapy. For patients with symptoms that do not respond to psychotherapy, who are not suitable for psychotherapy or who still have severe functional impairment after an adequate trial of psychotherapy, pharmacological treatment should be planned. In case of partial response to psychotherapy, the clinician should consider combining psychotherapy with drug treatment.

Given their efficacy, adverse effect profile and ease of use, SSRIs are the first-line pharmacological treatment for children and adolescents with dysthymia, even though further studies are needed to confirm their acute and long-term efficacy (the safety of paroxetine is currently under investigation). Other medications (i.e. TCAs or bupropion) should be considered in case of nonresponse or comorbidity.

According to clinical experience and clinical guidelines for depressive disorders in children and adolescents,[32,42] psychoeducational interventions and psychosocial support should be provided to parents and other caregivers during the acute-treatment phase to help them manage the child's irritable mood and foster a therapeutic alliance and better compliance with treatment during both pharmacotherapy and psychotherapy.

When evaluating the response to the acute-phase intervention and planning the continuation phase, a careful evaluation of functional improvement (not only the improvement of depressive symptoms) is needed. The authors believe that during the continuation phase, the introduction of CBT or 'booster' sessions to consolidate the skills learned in the acute phase could be the best way to prevent relapse and long-term sequelae.[38,90,107]

So far, most acute studies have focused on the symptom profile; more information should be gathered on the profile and changes concerning the de-

gree of psychosocial impairment of children with dysthymic disorder. Given the lack of data about the response pattern after the acute phase of treatment, prospective evaluation of response in children and adolescents with dysthymic disorder in the continuation phase is another primary need in the field.

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