REVIEW ARTICLE

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A Risk-Benefit Assessment of Pharmacotherapies for Clinical Depression in Children and Adolescents

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Abstract

Child and adolescent major depressive disorders are common and recurrent disorders. The prevalence of major depressive disorders is estimated to be approximately 2% in children and 4 to 8% in adolescents. Major depressive disorders in children are frequently accompanied by other psychiatric disorders, poor psychosocial outcome and a high risk of suicide and substance abuse, indicating the need for effective treatment and prevention.

The use of antidepressant medications as the first line of treatment for children and adolescents with mild to moderate major depressive disorders has been questioned. However, some subgroups of patients may benefit from initial treatment with antidepressants. These subgroups may include patients who are unwilling or unable to undergo psychotherapy, have not responded to at least 8 to 12 sessions of psychotherapy, have bipolar, atypical or severe depression or have recurrent depression.

Currently, the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors are the first medication choice because of their efficacy, benign adverse effect profile, ease of use and low risk of death following an overdose.

Further research in continuation and maintenance treatments, treatment of comorbid conditions, subtypes of depression, e.g. bipolar, atypical, seasonal, and combinations of pharmacotherapy and psychotherapy are needed. In addition, studies of the pharmacokinetics, pharmacodynamics and long term adverse effects of antidepressant medications in children and adolescents are warranted.

Child and adolescent major depressive disorders are common and recurrent disorders. The prevalence of major depressive disorders is estimated to be approximately 2% in children and 4 to 8% in adolescents.[1-8] Major depressive disorders in children and adolescents are frequently accompanied by other psychiatric disorders, poor psychosocial outcome and a high risk of suicide and substance abuse, indicating the need for efficacious treatments and prevention. The use of antidepressants in the treatment of child and adolescent depression appears reasonable in light of the significant morbidity and mortality associated with this disorder, the multiple lines of evidence suggesting continuity from child and adolescent to adult depression and the well established efficacy of antidepressants in the treatment of adult depression.

While the goal of this article is to address the risk-benefit issues related to the pharmacological treatment of major depressive disorders in childhood and adolescence, all the studies in children have focused on major depressive disorders and none on dysthymic disorder. However, general principles for the pharmacological treatment of major depressive disorders may also be applied to the treatment of dysthymia.

Although it is beyond the scope of this review, it is important to mention that 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 depressive disorders.

1. Psychopharmacological Interventions

An acute phase medication trial usually lasts at least 6 to 12 weeks, during which patients are seen weekly or biweekly for monitoring of symptoms, adverse effects, dose adjustments and psychotherapy.

Most of the studies published in the child and adolescent literature to date have evaluated the effects of the tricyclic antidepressants (TCAs) and few have addressed the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs). Other antidepressants, including the heterocyclics (e.g. amoxapine, maprotiline), amfebutamone (bupropion), venlafaxine and nefazodone, have been found to be efficacious for the treatment of adults with depression,[9] but they have not been studied for the treatment of children and adolescents with depression.[10]

Factors to consider when selecting an antidepressant include the patient's subtype of depression, chronicity of symptoms and past treatment history, as well as the medication's likelihood of adverse effects, safety in overdose and cost.[11] Before using antidepressants, parents and patients should be informed about adverse effects, dose and the lag time before onset of therapeutic effects. Prior to starting medication treatment, it is advisable to assess the severity of the depressive symptoms using one of the available depression rating scales (e.g. Beck Depression Inventory),[12] and assess the existence of physical signs and symptoms that resemble medication adverse effects. Patients and parents should be informed about the danger of an overdose, in particular with TCAs. For patients at risk of suicide, we recommend that parents be responsible for storing and administering the medications, especially during the acute episode of depression and during the first 2 to 4 months after complete remission.

A medical history and examination are indicated before using antidepressants. Use of other medications that may interact with the antidepressants and history of allergies should be ascertained. Thus far,

there has been no need for baseline laboratory testing before using SSRIs. As we will discuss in more detail in section 1.2, before starting one of the TCAs, a baseline electrocardiogram, resting blood pressure and heart rate (supine or sitting, standing) and bodyweight should be obtained. No other tests are generally indicated in a healthy child before starting antidepressants.

1.1 Selective Serotonin Reuptake Inhibitors (SSRIs)

In children and adolescents, SSRIs are favoured as first-line medications for treatment of depression for a number of reasons. SSRIs are efficacious for the treatment of all ages with major depressive disorders.[11,13,14] SSRIs have a relatively acceptable adverse effect profile, very low lethality after an overdose and easy administration (generally once a day). In fact, despite the paucity of research with the SSRIs, the use of SSRIs for the treatment of depressed children and adolescents has increased rapidly over the past few years. IMS America noted an increase of 69% in the total number of prescriptions of SSRIs for children and adolescents from 1995 to 1996.[15]

The SSRIs have been shown to selectively block the presynaptic neuronal reuptake of serotonin with little or no affinity for the adrenergic, cholinergic or histaminic receptor.[13,16] SSRI relative potency to block serotonin reuptake has been reported to be: citalopram > paroxetine > fluvoxamine > sertraline > clomipramine > fluoxetine.[16] However, potency has not been shown to be correlated with clinical improvement.[16]

Noncomparative studies have reported that 70% to 90% of adolescents with major depressive disorders experienced an improvement in depressive symptomology with fluoxetine or sertraline.[16,17] A double-blind, placebo-controlled study in a very small sample of adolescents with major depressive disorders did not find significant differences between placebo and fluoxetine.[18] However, a recent 8-week, double-blind study involving a large sample of youths with major depressive disorders showed that a significantly greater number of children and adolescents experienced an improvement in depressive symptomology with fluoxetine than to placebo (58% *vs* 32%, as measured by the Clinical Global Improvement Scale).[14] Despite the significant response to fluoxetine, many patients had only partial improvement in their symptoms of depression and only 31% experienced a full remission. A possible explanation for many patients experiencing only a partial improvement is that effective treatment may involve variation in dose or length of treatment. Also, it is possible that the ideal treatment may involve a combination of pharmacological and psychosocial treatments.

A preliminary analysis of a multicentre study in outpatient adolescents comparing paroxetine, imipramine and placebo (n = 270) for the treatment of major depressive disorders also suggested that paroxetine was efficacious and well tolerated.[19]

1.1.1 Adverse Effects

The adverse effects of all SSRIs are similar, dose-dependent and may subside with time.[13] One of the main adverse effects is so-called 'behavioural activation', which manifests as agitation, impulsiveness, silliness and 'daring' behaviours. It needs to be differentiated from mania, given that, similar to other antidepressants, the SSRIs may trigger an episode of hypomania or mania in vulnerable patients. In addition, the SSRIs may induce gastrointestinal symptoms (e.g. nausea, diarrhoea), decreased appetite, decreased or increased bodyweight, headaches (and migraines in patients with family history), restlessness, tremor, jitteriness, insomnia or hypersomnia (in particular paroxetine and fluvoxamine), diaphoresis, vivid dreams, sexual dysfunction (delayed ejaculation, anorgasmia), disruption of sleep architecture, apathy and indifference.

The SSRIs may also induce extrapyramidal symptoms (e.g. akathisia), in particular when combined with antipsychotics).[20,21] In rare cases, SSRIs have been associated with hyponatraemia[22] and with ecchymoses.[23-25] Allergies have been reported but, as with any other medication, these need to be differentiated from allergies to the dyes contained in the medication preparation.

Table I. Pharmacokinetic parameters and dosage recommendations for selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (based on studies in adults, except for Findling et al.[32])

Drug	Time to peak plasma concentration (h)	Plasma half-life		Inhibition of own metabolism	Active metabolites	Initial dosage (mg/day)	Dosage range (mg/day)
		single dose	multiple dose				
Fluoxetine	6-8	2 days	6 days	Yes	Norfluoxetine (half-life 7-15 days; after treatment for 2-3 mo concentrations are 2-3 times higher than those of fluoxetine)	5-10	10-60
Sertraline	4-8	1 day	1 day	No[a]	Desmethylsertraline (mildly active)	25-50	50-200
Paroxetine[32]	3-8	16h	1 day	Yes	Metabolites are active at higher doses	10-20	10-60
Fluvoxamine	2-8	16h	1 day	Yes (mildly)	Fluvoxamine acid (mildly active)	25-50	50-300
Citalopram	2-4	33h	33h	No[a]	Desmethylcitalopram and didemethylcitalopram	10-20	10-60

a Linear pharmacokinetics.

SSRIs, in particular fluoxetine, were initially thought to be associated with increased risk for suicide (perhaps linked to behavioural activation or akathisia).[26,27] However, while not ruling out such phenomena in a small number of cases, several studies and a recent meta-analysis suggest that SSRIs reduce the risk of suicide in depressed patients.[28] It is important to underline that most studies of SSRIs in children and adolescents have focused on acute adverse effects with no studies evaluating the long term adverse effects.

1.1.2 Prescribing SSRIs

We recommend starting with a lower dose of an SSRI and increasing it progressively. A slow, but steady approach may reduce the likelihood of inducing adverse effects (particularly in patients with comorbid panic disorder) which could jeopardise patient and parents' compliance with treatment. Fluoxetine takes a longer time to reach steady state plasma concentrations and may require longer trials. However, it appears that, in adults, steady state pharmacokinetics are not required for clinical efficacy.[29]

All SSRIs seem to be equally efficacious for the treatment of major depression and they have similar adverse effects. Currently, it appears that no recommendations can be made as to the choice of particular SSRI to use. However, they have some differences, including elimination half-lives, drug interactions and antidepressant activity of their metabolites.[13,16,30,31] Time to peak concentration after ingestion, plasma half-life, doses and metabolites, based on studies in adults, are outlined in table I. It is important to emphasise that individual patients may respond differently to some SSRIs.

The time course of improvement with the SSRIs appears to be similar to that of the TCAs (4 to 6 weeks). Therefore, guidelines to change dosages of TCAs described in section 1.2.3 may be applied for the SSRIs. However, these guidelines need to be applied cautiously because it is not clear if longer trials with SSRIs will reveal an increase in the number of patients with late improvement.[33] Patients receiving standard dosages have similar probabilities of responding as those on higher dosages.[34,35] However, individual patients may need higher doses to achieve responses.

1.1.3 Pharmacokinetics and Blood Concentrations

A pharmacokinetic study in children and adolescents showed that after 8 weeks of treatment, concentrations of fluoxetine and its metabolite norfluoxetine had not reached steady state,[36] suggesting that clinical efficacy studies using this drug must last 12 weeks or more. This study exemplifies the importance of studying the pharmacokinetics of psychotropics in children and adolescents before embarking on clinical efficacy studies be-

cause, as in the case of medications with long half-lives, shorter studies may not find differences between the medication and placebo. Interestingly, however, preliminary analysis of a recent study suggested that the half-life of paroxetine may be shorter in children and adolescents than in adults.[32]

Overall, the SSRIs possess a relatively flat dose-response curve suggesting that maximal clinical response may be achieved at minimum effective dosages. Thus, allowing adequate time to reach a clinical response is preferable to increasing dosages repeatedly. In the absence of a serious concern about toxicity or unless checking for compliance, monitoring of plasma SSRIs concentration is not indicated.[13,30,31]

1.1.4 Discontinuation

SSRIs with shorter half-lives, e.g. paroxetine, may induce withdrawal symptoms when discontinued abruptly; these symptoms may mimic a relapse or recurrence of a depressive episode, e.g. tiredness, irritability.[37] Furthermore, there is preliminary evidence that rapid discontinuation of an antidepressant may induce a relapse or recurrence of depression. Therefore, if these medications need to be discontinued, they should be tapered over time.

1.1.5 Interactions with Other Medications

All SSRIs inhibit, in various degrees, the metabolism of many medications that are metabolised by the hepatic cytochrome P450 (CYP) isoenzymes. Some well known medications that interact with SSRIs include: the TCAs, antipsychotics, antiarrhythmics, some anticonvulsants, some β-blockers and calcium antagonists, cisapride, benzodiazepines, carbamazepine, theophylline, warfarin, terfenadine and astemizole.[13,16] This is not an exhaustive list and new interactions are frequently discovered. The reader is urged to consult additional sources and stay abreast of new information about interactions. When using SSRIs in combination with other medications, we recommend being cautious with dosage administration, paying close attention to any symptoms which could indicate toxicity, and monitoring of blood concentrations of medications with low therapeutic indices.

Interactions with other serotonergic medications, e.g. monoamine oxidase inhibitors (MAOIs), may induce the serotonergic syndrome, characterised by agitation, confusion, hyperthermia, etc. It is important to emphasise that MAOIs should not be given within 5 weeks of stopping fluoxetine and within at least 2 weeks for other SSRIs. Also, the SSRIs should not be administered within 2 weeks of stopping MAOIs. Lithium is also a serotonergic compound and, while all possible interactions with SSRIs should be monitored carefully, this possible interaction has not been well studied.[38,39] The SSRIs also have a high rate of protein binding, which can lead to altered therapeutic or toxic effects of other highly protein-bound medications.

1.2 Tricyclic Antidepressants

Randomised controlled studies in adults with major depressive disorder have consistently confirmed the efficacy of TCAs, with 50 to 70% of patients receiving TCAs achieving an improvement in depressive symptoms and drug-placebo differences ranging from 20 to 40%.[9,40] In contrast, in children and adolescents with depression, 12 double-blind psychopharmacological trials showed that 50 to 60% of patients experienced an improvement in depressive symptoms with both TCAs (nortriptyline, desipramine, amitriptyline) and placebo.[41-43] Furthermore, a recent large multicentre study showed no differences between imipramine and placebo in a large group of adolescents with depression.[19]

These findings suggest that the TCAs are not useful in the treatment of children and adolescents with depression. However, TCAs may be indicated in certain individual cases, for example to augment the effects of SSRIs and for treatment of a child with major depressive disorder and attention deficit hyperactivity disorder (ADHD).

1.2.1 Adverse Effects

Most studies in children have focused on the short term adverse effects of TCAs, with few studies describing the long term adverse effects. TCA

adverse effects are mainly caused by blockade of cholinergic, histaminic and adrenergic receptors.[44] Anticholinergic adverse effects include dry mouth (and as a consequence, dental cavities), impaired ability to focus vision at close range, constipation and urinary hesitation. Adrenergic blockade may cause orthostatic hypotension and fainting. TCAs may also induce sedation, bodyweight gain, dizziness, lowered seizure threshold, myoclonus or a confusional state. As with other antidepressants, the TCAs may trigger a switch to mania.[45] Patients and their families should be educated about the symptoms of mania or hypomania and instructed to call their clinicians if these symptoms appear. At therapeutic dosages it appears that the TCAs do not affect short term memory or cognitive functions,[46] but distinct cognitive disturbances have been reported with high concentrations of TCAs.[47]

The most common cardiovascular adverse effect of TCAs is sinus tachycardia, affecting approximately one-third of children and adolescents treated with these agents.[48] Although heart rates below 130 beats/minute in children and 120 beats/minute in adolescents are considered normal, the long term clinical or haemodynamic significance of mild tachycardia is not known.[49] Other cardiovascular adverse effects include high blood pressure, orthostatic hypotension, prolongation of the PR, QRS, QT and QTc intervals and, more rarely, cardiac arrhythmias.[48] Some of these adverse effects may be minimised by slowly increasing the dosage of the TCA or, if effects do occur, by reducing the dosage.

TCA treatment should be carefully considered and is sometimes contraindicated in the presence of significant conduction delays (e.g. atrioventricular delay or block, Wolff-Parkinson-White syndrome), cardiac structural abnormalities and significant rhythm disturbances. The use of TCAs should be considered with caution in persons with a personal or a family history of premature cardiac disease, sudden death, arrhythmias or syncope. In any of these circumstances, consultation with a paediatric cardiologist is advisable before starting a patient on a TCA.

1.2.2 Sudden Death and Tricyclic Antidepressants

In children, desipramine[50-54] and, possibly, imipramine[55,56] have been associated with sudden death. In adults, desipramine may have a higher risk of fatality after overdose than other TCAs.[57,58] These findings suggest that desipramine may be more toxic and associated with more cardiovascular adverse effects than other TCAs. In contrast, Wilens and colleagues[48] found that desipramine was not associated with a higher incidence of cardiovascular effects than other TCAs. Although controversial, a Task Force of the American Academy of Child and Adolescent Psychiatry[57] estimated that the relative risk of sudden death with desipramine in children was 2.5 times higher than the annual population base rate of 4.2 sudden deaths/million children in the US. In any case, if the TCAs are indeed associated with this phenomena, it is unclear whether close monitoring of cardiovascular parameters can reduce or prevent the risk of sudden death.

1.2.3 Prescribing Tricyclic Antidepressants

It is recommended that TCAs be started at low dosages to avoid the emergence of adverse effects and improve the adherence to treatment. Usually, the initial dosage is imipramine 10 to 25 mg/day or its equivalent. In adolescents, TCAs are generally administered once a day at bedtime to help with compliance and, when sedating TCAs are used, to help with sleep. Divided doses are used most commonly in children, as they metabolise TCAs more rapidly,[59] and in patients who experience adverse effects because of high blood peak concentrations. The dosage can be increased by 25mg every 5 to 7 days, as adverse effects allow. The final dosage chosen is that at which the patient has a therapeutic response without experiencing disturbing adverse effects. The maximum dosage for imipramine, desipramine and amitriptyline is 5 mg/kg/day (with a maximum dosage of 300 mg/day). Nortriptyline, being about twice as potent, has as its maximum dosage 2.5 mg/kg/day or a maximum of 150 mg/day.

Due to the fatality risk associated with TCAs in overdose, special caution should be taken in terms of the amount of medication prescribed at each appointment.

It is advisable to perform a baseline electrocardiogram and electrocardiogram rhythm strips after reaching dosages higher than 2.5 mg/kg/day for imipramine and desipramine and 1 mg/kg for nortriptyline. Thereafter, it is recommended that the rhythm strip be repeated after each dosage increase of 50 to 100 mg/day.

There have been as yet no studies in children and adolescents indicating the optimal time to increase the dosage or to change medications if the patient has not responded to treatment. A recent study in depressed adults[33] recommended that patients should be treated with adequate and tolerable doses of TCAs for at least 4 weeks. At 4 weeks, if there is not even minimal improvement in the patient's condition, e.g. a 25% reduction on the initial Hamilton Depression Rating Scale[60] or on the Beck Depression Inventory score,[12] then the patient's treatment should be modified (e.g. dosage increase, change medications). If the patient shows minimal improvement, they should continue the same dosage until completing at least 6 weeks of treatment. At this point, if no further improvement has been observed, other treatment strategies should be considered and the reader is referred to section 4 on treatment-resistant depression.

1.2.4 Pharmacokinetics and Blood Concentrations

Only a few studies have analysed the pharmacokinetics of TCAs in children and adolescents, e.g. Clein and Riddle,[59] Kye and Ryan.[43] The metabolism, distribution, half-life and protein binding of TCAs in children and adolescents appear to be different compared with in adults, underscoring the need to examine developmental differences in the pharmacokinetics of patients with early-onset mood disorders.[61] For example, children and adolescents display a more rapid metabolism of drugs, thereby requiring relatively larger doses for a given bodyweight than adults.[62] Children also have more efficient hepatic metabolism of drugs than adults, resulting in rapid deamination of TCAs and they can convert initially serotonergic tertiary-amine TCAs into less serotonergic secondary-amine TCAs.[43,59]

At any given oral dose, studies across the lifespan have shown marked interindividual differences in tricyclic antidepressant steady-state blood concentrations.[43,59] No correlations between plasma concentrations and clinical response have been reported in adolescents with major depressive disorder.[43,59] In contrast, in depressed children, it appears that a combined plasma concentration of imipramine and desipramine of >150 μg/L are associated with better response;[63,64] however, these results need further replication. Given the above-noted pharmacokinetic results, routine measurement of TCA concentrations in children and adolescents is controversial. In adults, the recommended blood concentrations in adults for imipramine and desipramine range between 150 μg/L and 300 μg/L. In adults, an inverted U-curve relationship between nortriptyline plasma concentrations (50 μg/L and 150 μg/L) and response has been reported.

We believe that instead of frequent measurement of blood concentrations, clinical observation is still the best method to achieve maximal benefit without producing intolerable adverse effects. However, measurement of TCA blood concentrations may be useful to assess compliance, confirm rapid metabolism, which often may be induced by other substances, e.g. anticonvulsants or cigarette smoking, and to assess slow metabolism which is usually present in about 10% of the Caucasian population.[59] Blood concentrations should be assessed after the addition of agents that may interact pharmacokinetically with TCAs, e.g. SSRIs, and before terminating a medication trial. They also should be obtained when there is concern about lack of response or worsening symptoms, as TCA toxicity can at times be mistaken for worsening depression. Blood concentrations should be obtained 10 to 12 hours after administration of the last oral dose.

1.2.5 Discontinuation

To avoid withdrawal adverse effects, it is recommended that dosages of TCAs be tapered gradually. It is also important to mention that it appears that rapid discontinuation of treatment may be associated with increased relapse or recurrences of depression.[65,66] Therefore, unless a TCA must be stopped for a clinically urgent reason, e.g. the presence of conduct delays, manic symptoms, etc., it is advisable to discontinue the medications progressively, possibly over a period of 6 weeks. Further research in this area is necessary.

1.2.6 Interactions with Other Medications

It is important to be aware of possible interactions between TCAs and other medications and substances that may worsen sedation [e.g. antihistamines, alcohol (ethanol), antipsychotics], hypotension (e.g. clonidine, low potency antipsychotics), anticholinergic adverse effects (e.g. antihistamines, low potency antipsychotics) and potentiate cardiac adverse effects (e.g. terfenadine).

Also, concentrations of TCAs can be varied with the use of other medications or substances. TCA blood concentrations may increase with coadministration of SSRIs, stimulants, certain antimicrobial agents [e.g rifampicin (rifampin), fluconazole and related antifungals, erythromycin and other macrolides], certain antiarrhythmics (e.g. quinidine, propafenone), some calcium antagonists (e.g. verapamil), thiazides and cimetidine. Concentrations may decrease with long term use of alcohol, carbamazepine and with heavy cigarette smoking.

When MAOIs have been used and a switch to TCAs is wanted, discontinuation of the MAOIs 10 to 14 days before starting TCA treatment is required. Also, new pharmacokinetic interactions (via the CYP hepatic metabolism system) between TCAs and other medications are being continually discovered and thus the reader is encouraged to stay abreast of changes noted in the literature.

1.3 Other Antidepressants

Very few studies exist on the use of other antidepressants [e.g. amfebutamone (bupropion), venlafaxine, nefazodone and MAOIs] in the treatment of depressed children and adolescents and most are uncontrolled.[67-69] A recent controlled double-blind study comparing venlafaxine and placebo in a small sample of children and adolescents with depression (n = 30) using small doses of venlafaxine (up to 75 mg/day) showed no differences in outcome or adverse effects between venlafaxine and placebo.[70] Venlafaxine has been found to be beneficial for treating ADHD symptoms in adults,[71,72] but so far this has not been shown in children and adolescents.[73]

Amfebutamone is effective for treating ADHD in children and adolescents.[74,75] Amfebutamone can be considered an alternative treatment for adolescents with depression and comorbid ADHD. A recent study showed that the pharmacokinetics of nefazodone are similar among adults, adolescents and children.[67,76] However, efficacy data for nefazodone in adolescents with depression have not been published.

1.4 Pharmacological Treatments of Major Depressive Disorder Subtypes

Subtypes of major depressive disorders, such as atypical, seasonal or bipolar depression, may require alternative treatments. No studies on atypical depression in children and adolescents have been published, but adults with atypical depression respond better to treatment with MAOIs, and possibly SSRIs, than to TCAs.[77-79] Studies in adults and one investigation in children and adolescents have shown that bright light therapy is efficacious in seasonal depression.[80-82]

Because the symptoms of unipolar and bipolar depression are similar, it is difficult to determine whether children and adolescents need only an antidepressant, or concomitant use of mood stabilisers. If clinical indicators of bipolar depression, e.g. psychosis, psychomotor retardation or a family history of bipolar disorder are present, the clinician should consider with the patient and family the pros and cons of initiating a prophylactic mood stabiliser. There are no pharmacological studies in adolescents with bipolar depression and few control-

led studies in adults. However, it has been recommended that treatment be initiated with a mood stabiliser [lithium, valproic acid (sodium valproate), or carbamazepine], given that antidepressants may induce mania.[83] If no response is observed, an antidepressant should be added to the treatment. Amfebutamone, SSRIs and MAOIs seem to give a better response in bipolar depression than TCAs. This may be related to their possible lower risk of inducing a switch from depression to mania and rapid cycling.[84-86] For patients presenting with mixed states (depression plus mania), the use of valproic acid instead of lithium should be considered.[87]

When depression is accompanied by psychotic features, the rate of recovery is better if antidepressants are combined with an antipsychotic.[88-90] Given the potential risk of tardive dyskinesia associated with the long term use of antipsychotics, these agents should be tapered soon after the remission of depression. The 'atypical' antipsychotics (risperidone, olanzapine, clozapine) may represent an alternative to classic antipsychotics, but further research is needed. In adults, electroconvulsive therapy has been found to be particularly effective for psychotic depression.[91] In addition, in adults, the best response has been associated with higher blood concentrations of TCAs.[90,92] Finally, there has not been sufficient research to definitively determine if the new antidepressants, including the SSRIs, demonstrate the same efficacy as the TCAs for psychotic and severe depressions.

2. Continuation and Maintenance Treatments

There are very few continuation and no maintenance studies in adolescents with depression. Thus, anticipating future research, most of the following recommendations outlined are based on adult studies. Given the high rate of depressive relapse and recurrence, continuation therapy is recommended for all patients and maintenance therapy should be considered for some patients.

2.1 Continuation Therapy

Successful acute phase pharmacotherapy or psychotherapy should be followed for at least 6 months by continuation treatment. However, symptomatic breakthroughs may prolong the continuation phase for as long as 9 to 12 months. During the continuation phase, the patient and the patient's family should be taught to recognise early signs of relapse. In addition, antidepressants must be continued at the same dose used to attain remission of acute symptoms, providing that there are no significant adverse effects or dose-related negative effects on the patient's compliance.[9,40,93] In adults, pharmacotherapy treatment during this phase reduces the risk of relapse from 40 to 60% to 10 to 20%.[93,94] TCAs, SSRIs and lithium have been found to be significantly more effective in preventing relapses than placebo. In some adult studies, >50% of patients randomised to placebo relapsed during continuation trials, most within 3 months of antidepressant discontinuation.[93,95,96]

If maintenance therapy is not required, at the end of the continuation phase the antidepressant dosage should be decreased gradually over 6 weeks or more to avoid withdrawal effects, e.g. sleep disturbance, irritability, gastrointestinal symptoms. The clinician could potentially misinterpret withdrawal effects as the need for continued medication. Rapid discontinuation of antidepressants may also precipitate a relapse or recurrence of depression. In children and adolescents, extended vacations are a good time to gradually discontinue medications.

2.2 Maintenance Therapy

The main goal of the maintenance phase is to prevent recurrences. This treatment period may extend from 1 year to indefinitely and usually commences after the patient has been asymptomatic for a period of approximately 6 to 12 months (continuation phase).

2.2.1 Maintenance Psychopharmacological Studies

Despite differences in methodology, several controlled trials comparing TCAs or SSRIs with placebo have shown that these antidepressants diminish the risk of recurrences of major depressive episodes in adult patients with unipolar depression.[93,97-99] In fact, early studies which used reduced dosages of TCAs reported that the rate of recurrence for patients taking placebo was more than twice that for active medication.[65,66] In contrast, new studies, using 'full dose' TCA maintenance dosages found a 5-fold medication-placebo difference.[65,66,97,99] Nevertheless, medications are not always efficacious and up to 25% of patients have recurrences. Apparently all antidepressants are equally useful for maintenance treatment in unipolar depression.[65,66,96-103] Although there are no published long term randomised controlled trials of the SSRIs, amfebutamone, nefazodone or venlafaxine in children and adolescents, some studies in adults with depression showed 1-year recurrence prevention rates of 80 to 90% with these agents.[100-103] There is controversy as to whether lithium and other mood stabilisers are useful for maintenance treatment of patients with depression.[104]

2.2.2 Who Should Receive Maintenance Therapy?

The recommendation for maintenance therapy depends on several factors related to the severity of the latest depressive episode, e.g. suicidality, psychosis, functional impairment, number and severity of prior depressive episodes, chronicity, comorbid disorders, family psychopathology, presence of support, patient and family willingness to adhere to the treatment programme and any medical contraindications to continued medication treatment.

In adults, it has been recommended that patients who experience only a single uncomplicated episode of depression, mild episodes, or a lengthy interval between episodes, e.g. 5 years, probably should not start maintenance treatment.[93] Otherwise, patients with 3 or more episodes, those with chronic depression,[9,40] or those patients who have experienced 2 episodes and who have 1 or more of the following criteria: (i) a family history of bipolar disorder or recurrent depression; (ii) early-onset of the first depressive episode (before age 20); and (iii) both episodes were severe or life threatening and occurred during the past 3 years,[9] should receive maintenance treatment. Given that depression in adolescents has similar clinical presentations, sequelae and natural course compared with adults, the above-noted guidelines probably apply to adolescents with depression. Clinicians should also consider that comorbid psychiatric disorders (anxiety, substance abuse), conflictive environments and residual or subsyndromal symptomatology are associated with high risk for recurrences.

2.2.3 Duration of the Maintenance Phase

Considering what has appeared in the medical literature concerning adult patients with depression,[40,93] it is recommended that adolescents who experience second episodes of depression should be maintained for at least 1 to 3 years on the same dosage of the antidepressant that was used to achieve clinical remission during the acute treatment phase. Patients experiencing second episodes of depression accompanied by psychosis, severe impairment, severe suicidality and refractory treatment or patients who experience 3 or more episodes, should be considered for longer or lifelong treatment.

2.2.4 Which Treatment?

Practically, unless there is any contraindication, e.g. medication adverse effects, the treatment that was effective in treating the acute episode should be used for maintenance therapy. Instead of maintaining patients on medications only, multimodal treatments should be offered to help the patients to cope with the 'psychosocial scars' induced by the depression and/or with environments charged with stressful situations. In children and adolescents, there have been a few noncomparative investigations with small samples of adolescents with depression which suggest that psychotherapy may be useful to prevent recurrences of major depression.[105-107]

3. Treatment of Comorbid Conditions

In addition to the treatment of depressive symptoms, it is of prime importance to treat the comorbid conditions that frequently accompany major depressive disorder. Forty to 90% of adolescents with major depressive disorders have other psychiatric disorders, with at least 20 to 50% having 2 or more comorbid disorders.[108-120] Most frequent comorbid diagnoses are dysthymic and anxiety disorders (occurring in 30 to 80% of adolescents with major depressive disorders), disruptive disorders (10 to 80%) and substance use disorders (20 to 30%).

Specific treatment guidelines for each of the comorbid psychiatric disorders should be considered. If it is possible, choose the medication that optimises response for both the depression and comorbid disorder. For example, TCAs and SSRIs may help both anxiety disorders and major depressive disorders in adults and children;[121-123] TCAs, amfebutamone and venlafaxine appear to be useful in treating other disorders such ADHD in adults and children;[74,124,125] and SSRIs may help in the treatment of bulimia and major depressive disorders, clomipramine and the SSRIs can help both depression and obsessive-compulsive disorders and both TCAs and SSRIs may help dysthymia and major depressive disorders.[126,127] Nevertheless, at times, it is necessary to use 2 medications to treat the 2 conditions, e.g. SSRIs and stimulants.

4. Treatment-Resistant Depression

In adults, the term treatment-resistant depression is used when there is a lack of response to antidepressants in patients who are accurately diagnosed, compliant with treatment and assessed with valid outcome measures.[128] Patients must have had at least 2 trials with 2 different classes of antidepressants, administered at standard doses for at least 6 weeks each. In contrast with adults with depression, there is no clear definition of treatment-resistant depression in adolescents with major depressive disorders.[129]

When managing patients with treatment-resistant depression the following reasons for treatment failure should be considered: inadequate drug dosage, inadequate length of drug trial, comorbidity with other psychiatric disorders (anxiety, dysthymic, substance use and personality disorders), comorbid medical illnesses, undetected existence of bipolar depression, exposure to chronic or severe life events such as sexual abuse, and incorrect diagnoses.[128,130] All of these conditions may require different modalities of therapy other than simply antidepressant treatment. Clinical observation suggests that sometimes after a medication-free interval (4 to 6 weeks), patients may respond to previously unsuccessful antidepressant trials. In addition, psychotherapeutic interventions also appear to be beneficial for adult patients with treatment-resistant depressions.[131,132]

4.1 Psychopharmacological Strategies

Several psychopharmacological strategies have been recommended for adults with treatment-resistant depression: (i) optimisation (extending the initial medication trial and/or adjusting the dose); (ii) switching to another agent from the same or a different class of medications, or augmentation or combination therapy, e.g. lithium, thyroid hormone; and (iii) use of electroconvulsive therapy.[9,128,130] Each strategy requires implementation in a systematic fashion, education of the patient's family and support from clinicians to avoid the development of hopelessness in the patient and family.

Placebo-controlled studies of the efficacy of alternative treatments for patients with treatment-resistant depressions are difficult to pursue for pragmatic reasons, e.g. small sample sizes, as well as the dilemma of offering placebo to patients with treatment-resistant disorders. Consequently, there are very few randomised controlled treatment trials and few noncomparative studies in adults[128] and children and adolescents.

One noncomparative study in adolescents with treatment-resistant major depressive disorder showed significant improvement of depressive

symptoms after augmentation of TCA treatment with lithium.[133] Nevertheless, another noncomparative study, using an historical control group, did not replicate this finding.[134] Two small nonblinded studies, one with fluoxetine[135] and a second with the MAOI phenelzine,[68] found these agents to be effective in the treatment of adolescents who did not respond to TCAs. Geller and colleagues,[136] in a group of adolescents with chronic and severe major depressive disorder, found that intravenous clomipramine was superior to placebo for adolescents with treatment-resistant depression.

Anecdotal reports have suggested that adolescents with treatment-resistant depression may respond to electroconvulsive therapy.[137-139] Interestingly, a recent randomised controlled trial comparing amitriptyline with placebo in a sample (n = 30) of 'treatment-resistant' depressed adolescents showed a 70% improvement for both treatments.[140]

5. Developmental Considerations and Compliance

5.1 Developmental Considerations

It is critical to consider key developmental factors such as age, gender and pubertal status and their impact on drug concentration and response. Age should be treated as a major variable in response and adverse effects. Also, puberty may affect the pharmacokinetics of medications, possibly via competition for hepatic drug-metabolising enzymes by gonadal hormones.[141] Because drugs are differentially distributed into body tissues depending on their solubility characteristics, estimation of the amount of fat or water in a given patient may be a key factor in understanding why that patient requires a certain amount of a given drug.

As an individual enters puberty, the amount of fat, water and lean body mass changes.[142-145] Because height is increased by approximately 25% and bodyweight is nearly doubled in adolescence, it is likely that drugs will be distributed in a different way than in childhood. Lean body mass, skeletal mass and body fat are equal per unit bodyweight in prepubertal boys and girls, but, by maturity, women have twice as much fat relative to total bodyweight as adult men. The peak lean body mass growth velocity in men occurs 2 years later than in women on average and coincides with peak height velocity.

Change in the volume of distribution (age-related decrease of total body water and extracellular water) of a drug is a predictable and important event and will affect the dose needed to achieve a certain concentration in children and adolescents. If the drug is distributed largely in body water, the dose for men may be higher than women after puberty, but similar before puberty. If the drug is fat soluble, mature women might require a higher dose than younger women or mature men.[146,147]

Finally, variables such as race, gender and variations in genetically determined polymorphisms of the CYP enzymes can influence the pharmacokinetics and pharmacodynamics of medications, in particular, in the paediatric population. However, few studies have systematically determined the exact timing or nature of the differences as related to children and adolescents.

5.2 Compliance

It has been stated that noncompliance may be among the most significant problems that medicine faces today.[148] Failure to comply with treatment may be devastating for the patient and may also affect the interpretation of clinical research and trials, and may increase healthcare costs.

There are several excellent literature reviews on adult patients' compliance with medication regimens.[149] In general, approximately 40% of adult patients who are receiving psychiatric medications are noncompliant. The limited experience from studies of long term TCA administration for affective disorders indicates that adult patients' compliance is a major factor for ensuring continued response. It has been estimated that 70% of depressed patients taking TCAs fail to take 25 to 50% of their prescribed dose.[149] About 40% of patients who are receiving what should be adequate

dosages of oral TCAs have concentrations in plasma outside the therapeutic range.[149] Similar data with SSRIs have not been published. Objective compliance assessments have not yet been completed systematically with paediatric populations.

The assessment of compliance in pharmacological studies is critical as otherwise the value of a pharmacotherapeutic regimen cannot be assessed. For example, if the dose interval was correct but only half of each prescribed dose was taken, the response is likely to be 50% of that predicted with a much higher variability in clinical outcome. For oral dose administration, attenuation of effect as a result of imperfect compliance resembles the attenuation due to reduced bioavailability. In pharmacological terms, the dose-response curve is shifted to the right, just as though a competitive antagonist had been administered at the same time. Poor compliance in clinical research studies, though unlikely to occur consistently to this degree, could result in a new medicine being judged less potent than it really is and thus the recommended dose range would be too high. Furthermore, in comparative efficacy studies involving more than 1 drug per treatment arm, nonuniform and/or differential compliance among arms may increase the risk of a misinterpretation in findings.

6. Conclusions

In summary, in children with depression, the choice of the initial acute therapy depends on several factors including symptom severity, number of prior episodes, chronicity, subtype of depression (e.g. psychotic, bipolar, atypical), age of the patient, contextual issues (family conflict, academic problems, exposure to negative life events), patient compliance with treatment, previous response to treatment and patient and family motivation for treatment (e.g. adolescents may be reluctant to participate in family therapy, an anxious parent and patient may refuse medications as the first line of treatment, etc.) Also, clinician motivation and expertise to perform any specific therapy can affect the outcome of the treatment.[150,151]

Research into the pharmacological treatment of major depressive disorders in children and adolescents is relatively preliminary. Psychotherapy strategies (in particular cognitive-behavioural therapy) have been shown to be efficacious for the treatment of children and adolescents with mild to moderate depressions.[152] Thus, we would recommend initially at least an 8 to 12 week trial of psychotherapy. For patients whose depression does not respond, or who are not suitable for psychotherapy, and for patients with severe depression, psychosis, nonrapid cycling bipolar depression, a trial with an antidepressant is indicated. In this case, given their efficacy, benign adverse effect profile and low risk of death after an overdose, the SSRIs are the first choice of antidepressant.[10] However, TCAs or other medications such amfebutamone may be indicated in cases where comorbid ADHD is present.

Given the chronicity, recurrence and psychosocial consequences of childhood major depressive disorders and dysthymia, further research in child and adolescent continuation and maintenance treatments is needed. Also, studies on the treatment of comorbid conditions, subtypes of depression (e.g. bipolar, atypical, seasonal) and combinations of pharmacotherapy and psychotherapy are warranted. Finally, further studies in developmental considerations, prevention, pharmacokinetics, pharmacodynamics and antidepressant long term adverse effects in this population are also warranted.

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