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SHORT REVIEW

Pharmacotherapy in depressed children and adolescents

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Abstract

In children and adolescents, antidepressants are used in the treatment of depressive symptoms and several other psychiatric conditions. In the treatment of mild and moderate depressive symptoms, non-pharmacological approaches such as psychotherapy play a major role, a severe symptomatology may demand a combination with antidepressants. As first-choice medication for the treatment of juvenile depression, the selective serotonin reuptake inhibitor (SSRI) fluoxetine is recommended, due to its efficacy and approval. As second-choice antidepressants the SSRIs sertraline, escitalopram and citalopram might be used. Other antidepressants – such as tricyclic antidepressants, \( \alpha_2 \)-adrenoceptor antagonists, selective noradrenaline reuptake inhibitors (SNRI) – may be alternatively used, but not as first- or second-choice medications. In the case of “off-label” use, patients and parents have to be carefully informed prior to the start of medication, after a thorough risk–benefit analysis. In the following overview we address a general framework, therapeutic strategies and the issues of antidepressant pharmacotherapy for the treatment of unipolar depression in childhood and adolescence.

Key words: Antidepressants, depressive episode, child and adolescent psychiatry, selective serotonin reuptake inhibitor, tricyclic antidepressant

Introduction

The chemically and pharmacologically heterogeneous class of antidepressants are nowadays used not only in the treatment of depressive symptoms, but in diverse child psychiatric disorders, such as obsessive compulsive disorder (OCD), anxiety disorders, eating disorders, mutism, attention deficit/hyperactivity disorder (ADHD), enuresis and posttraumatic stress disorder (PTSD). In the following overview, however, our focus will be the use of antidepressants with the indication unipolar depression.

In adults, antidepressants exhibit a positive effect on the whole set of depressive symptoms, such as a low mood, irritability, reduction of energy, low self-esteem, feeling of hopelessness, psychomotor retardation, loss of interest and pleasure in normally enjoyable activities and social withdrawal. Antidepressive drugs improve somatic symptoms and loss of libido in the context of depression as well as agitation, low appetite and sleep disturbances. Major target symptoms are also suicidal ideations (Baldessarini 1989; Mulrow et al. 1998; Edwarts and Anderson 1999). In meta-analyses on the treatment of juvenile depression, however, limited efficacy of antidepressants in short-term randomised controlled trials was reported; especially in the age group of children (Schulte-Markwort et al. 2008; Tsapakis et al. 2008). Possible explanations for these observations might include developmental aspects of the brain and a higher response rates to placebo and other non-specific interventions in children compared to adolescents and adults (Tsapakis et al. 2008). Additionally, results have to be interpreted with caution as there are major study limits such as missing subgrouping into child- and adolescent- as well as gender-groups, inadequate dosing with lack of data on corresponding plasma concentrations, inadequate treatment duration, etc.
General framework of therapy

Depressive symptoms always demand a multimodal treatment including psychoeducation and psychotherapeutic interventions. Psychotherapy alone may be sufficient in mild to moderate depression, in the case of severe symptoms of major depressive disorders (MDD) mostly the combination with an antidepressant pharmacology is needed. Before starting with antidepressants, organic diseases, drug abuse, side effects, as well as intoxication have to be ruled out as underlying cause of symptomatology. Depending on severity of symptoms the clinical setting has to be chosen. In case of acute suicidality a treatment on the intensive ward may be necessary. In the onset of therapy, the child and the persons having care and custody have to be thoroughly informed about diagnosis and treatment options.

Pharmacotherapy of depressive symptoms in childhood and adolescence

Treatment strategies

Frequently antidepressants are used “off-label” in children and adolescents, they are prescribed without official approval. When informing about an intended drug treatment, the “off-label” use has to be explicitly referred to, the explanatory discussion and informed consent by patient and/or parent has to be well documented and written informed consent gained.

In terms of selection of the substance, the specific profiles of effects, side effects and potential interactions as well as the patient or family history on antidepressant response should be considered. In case of suicidal ideations an initial sedation and anxiolysis with a comedication of benzodiazepines and a thoroughly controlled initiation of antidepressants are necessary; furthermore agreement on an emergency plan in the outpatient setting in case suicidal urges are getting too strong, perhaps even an initial treatment on the intensive ward. In order to find the optimal treatment, the dosage of all antidepressants should be very carefully and stepwise increased in order to avoid seizures and drug-induced delirium. If available, for dosage optimization, control of drug interactions as well as in the case of non-response a therapeutic drug monitoring (TDM) should be performed in the steady state (Laux et al. 2007; Gerlach et al. 2009). In general, the antidepressant effect is seen after 1–4 weeks of treatment, sedation and improvement of sleep disorders already before that. After the first or second episode of unipolar depressive symptoms, a minimum of 6 months of antidepressant therapy with the finally effective dosage is recommended. In case of subsequent symptom remission a slow drug tapering for about 25% of the dosage per week may be initiated to minimize the risk of withdrawal symptoms.

In the case of non-response after monotherapy at a sufficient dose over 4–6 weeks, after revision of diagnosis and treatment compliance, an antidepressant with a different profile should be chosen. But changing from one to another SSRI might be beneficial. If antidepressant monotherapy stays ineffective, results from studies on adult patients might be carefully interpreted for potential augmentation strategies in children; e.g., with atypical neuroleptics (off-label use!), a mood stabilizer or a combination of two antidepressants (such as, e.g., an SSRI with a tricyclic antidepressant or mirtazapine) under thorough monitoring of potential interactions and side effects (Carvalho et al. 2007; Schmauss and Messer 2007).

For a long-term treatment or phase prophylaxis, substances such as lithium, carbamazepine, oxcarbazepine, valproic acid or lamotrigine are proven to be beneficial in adults. For this indication in children – after at least three episodes of unipolar depression, especially in presence of severe symptoms, psychotic features and suicidality – most studies exist for lithium (Campbell and Cueva 1995; Weller and Weller 2000; Gerlach et al. 2006). Due to its low therapeutic index, serum concentrations for this indication should be 0.6–0.8 mmol/l and regularly controlled by TDM.

Antidepressants of choice for the monotherapy of unipolar depression

The antidepressant of choice is fluoxetine due to its efficacy, proven repeatedly by randomized-controlled studies, already in children younger than 12 years (Emslie et al. 1997, 2002, 2008; Bridge et al. 2007) and its authorization by the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for the treatment of depression in subjects from the age of 8 years on. In off-label use, second choice antidepressants are SSRI such as sertraline, citalopram and es-citalopram, the eutomer of the racemic drug citalopram. As alternatives, but not antidepressants of first or second choice – due to their potentially severe side effects – tricyclic antidepressants and α₂-adrenoceptor antagonists may be used, the latter especially in the treatment of agitation and sleep disturbances connected to depression. Although study results on the safety of the selective noradrenalin-reuptake inhibitor (SNRI) venlafaxine are not yet finally resolved, a positive treatment effect is seen in adolescents, but not in children (Emslie et al. 2007). The effect of St. John’s Wort has not yet
been studied in controlled trials. A positive effect in the treatment of mild depression might be achieved (Simeon et al. 2005; Jorm et al. 2006); however, accompanied by a high potential of pharmacological interactions (Kölich and Fegert 2006). There are also no findings from controlled trials on monoamine oxidase inhibitors, which nowadays play a minor role in the treatment of juvenile depression due to their potential of severe interactions and side effects.

**SSRIs as first and second choice antidepressants in the treatment of unipolar depression**

The efficacy of the SSRI fluoxetine in treating juvenile depression has been proven in several controlled studies (Emslie et al. 1997, 2002, 2008; TADS team 2009). However, SSRIs in general show higher effect sizes in the treatment of anxiety disorders and OCD in childhood and adolescence, compared to depression (Bridge et al. 2007). Sertraline, citalopram and escitalopram are reported in some trials to be superior to placebo (Papanikolaou et al. 2006; Pössel and Hautzinger 2006; Wagner 2005; Wagner et al. 2003, 2004); however, their overall effectiveness according to the review of present study results is suggested to be limited (Tsapakis et al. 2008). They may be used as antidepressants of second choice, e.g., when fluoxetine does not show a treatment effect.

A controversial debate on a potentially increased risk of suicidality under SSRI treatment started with results of the FDA meta-analysis on 24 placebo-controlled studies on the use of antidepressants in children and adolescents (Hammad et al. 2006; Andrade et al. 2006). As SSRI may trigger behavioural activation – significantly more in children and adolescents compared to adults (Safer and Zito 2006) – they might facilitate the realization of suicidal impulses. In the FDA meta-analysis, a nearly two-fold increased risk of suicidal events under SSRIs was reported. After re-analysing the data and according to the newest meta-analyses, however, SSRIs show an acceptable risk–benefit relationship in the treatment of depression. Furthermore, in none of the former trials were completed suicides reported (Bridge et al. 2007; Fegert and Herpertz-Dahlmann 2005; Pössel and Hautzinger 2006). The combination of psychopharmacology and psychotherapy additionally seems to minimize the emergence of suicidal ideation (March et al. 2007). Safety in the case of overdose is still a strong argument favouring SSRIs over tricyclic or α₂-adrenoceptor antagonists in patients with unclear suicidality.

Although SSRIs are in general safe and well tolerated in children and adolescents (Fleischhaker et al. 2003), initially in the treatment the potential increase of behavioural activation, moodiness, suicidal thoughts, anxiety and sleep problems should be thoroughly monitored. As children often resorb and metabolize faster than adults, higher dosages than recommended for adults might be necessary. For most of the SSRI one dosage in the morning is sufficient, only fluvoxamine should be administered twice a day due to its half-life of 10–22 h. Fluoxetine might be started with (5–) 10 mg/day depending on the age and weight of the patient and increased every 5–7 days for 5–10 mg. For most children/adolescents 20 mg in the morning are effective, in case of insufficient response dosage might be increased up to 40–60 mg/day. For therapy of OCD and bulimia higher dosages are needed than for treating depression.

Toxicity of SSRI is low and rarely a serotonin syndrome occurs, however with – in the course – potentially life-threatening arrhythmia, seizures and coma. In case of a central serotonin overactivity, SSRI have to be discontinued immediately and intensive care might be needed. Pharmacokinetic interactions of SSRI with legal and illegal drugs and food have to be considered and have been discussed elsewhere in extensor (Lane 1996).

SSRI should be thoroughly discussed and carefully monitored in patients with epileptic seizures, brain damages, suicidality and comedication with drugs that might increase central serotonin activity and not be utilized in case of intoxication with sedating agents. If tapering is necessary, dosage should be reduced slowly, especially of those SSRI with a short half-life. Before starting an SSRI, in the first month of treatment and in the course, each 6 months, controls of blood pressure, heart rate and routine blood tests should be performed. Additionally, if clinically indicated, an EEG and ECG should be performed; the ECG necessarily in case of pre-existing cardiac problems or a positive family history for cardiac disorders.

**Alternative antidepressants in the treatment of monopolar depression**

Tryptic antidepressants did not show benefit, or only limited efficacy in comparison to placebo in the treatment of child and adolescent depression (Hazell 1995, 2002; Ambrosini 2000; Papanikolaou et al. 2006; Tsapakis et al. 2008). The lacking proof of efficacy might though be due to above-mentioned methodological study limitations. Clinical experience supports tricyclic antidepressants to be effective alternatives in the treatment of MDD. However, due to the potentially serious side effects, including cardiotoxic effects, and higher risk of intoxication they are not antidepressants of first or second choice. They might be used in patients with lethargy (e.g., clomipramine) and serious sleeping problems in the context of depression (e.g., doxepine). After starting
with a low dose, dosage might be increased every 4–5 days. Due to their long half-life a single intake in the morning or at night is sufficient.

If suicidal ideation is suspected, tricyclic antidepressants should not at all be prescribed or just in small amounts under narrow monitoring, as already a dose “3 times the normal” might cause life-threatening side effects. Overdosage leads to increased anticholinergic effects, finally with central temperature increase, tachycardia and arrhythmia, symptoms of delirium, seizures, somnolence and coma. Central anticholinergic syndrome demands immediate drug discontinuation and intensive care. The risk of side effects due to tricyclic antidepressants may be reduced by prescribing long-acting formulas. Tricyclic antidepressants interact with other antidepressants, anticholinergics, contraceptives, mood stabilizers, neuroleptics and methylphenidate, causing altered serum concentrations, partly increased side effects or reduced effectiveness. Smoking seems to alter serum levels of at least some antidepressants (Lind et al. 2009).

In the case of cardiac diseases the use of tricyclic antidepressants is strongly limited. The FDA describes the following events as serious: a QRS interval >30% of the norm or >120 ms, PR interval >200 ms, systolic blood pressure >140 mmHg or diastolic >90 mmHg, heart beat in rest >130/min. Treatment has to be carefully considered and monitored in case of comedication with sedating drugs, pre-occurring seizures and myoclonia (decreased seizure threshold), bipolar disorder (induction of mania) and suicidality (initially activating effect). A rushed tapering may lead to deteriorated mood and symptoms such as fever, sweating, headache and muscle pain, nausea and anxiety.

Before initiation of the tricyclic antidepressant, repeatedly in the first month, later every 3 and 6 months, controls of blood pressure, pulse and blood tests as well as an ECG and EEG are necessary. Furthermore, the patients’ history and family history for cardiac diseases, especially sudden unexplained deaths, have to be taken.

The α2-adrenoceptor antagonists, such as mianserine and mirtazapine are mainly indicated in anxious and agitated depression with associated sleeping problems, as from non-controlled studies a positive effect on depressive symptomatology including sleep problems has been reported (Dugas et al. 1985; Schlamp 1999; Haapasalo-Pesu et al. 2004). Mirtazapine, e.g., may be started at 15 mg and slowly increased to 45 mg, a single dosage per day is sufficient. Main side effects, especially at the beginning of treatment, are sedation and reduced reaction time, further possible side effects are discussed elsewhere (Masand and Gupta 2002). An advantage of this substance class might be the reduced potential for sexual dysfunction.

In controlled studies the SNRI venlafaxine has been shown to be clearly effective in depressed adults (Smith et al. 2002). In children, no benefit in comparison to placebo could be reported; however, a positive effect in adolescents was observed (Mandoki et al. 1997; Courtney 2004; Emslie et al. 2007; Bailly 2008). Due to a potentially increased risk of suicidal ideations and lack of approval, venlafaxine is at the moment not an antidepressant of first or second choice in juvenile depression.

For adults, initial dose is 37.5 mg with stepwise increasing dosage for 37.5 mg if needed. There is no official dose recommendation in children and adolescents. From our clinical experience in children, a standard dose of 37.5–75 mg, and in adolescents 75–150 mg might be used. Long-lasting formulas may reduce possible side effects of sedation, agitation, weight gain, sleep problems, vegetative symptoms, sexual dysfunction, etc.

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Statement of Interest
None.

References
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