Pharmacological Treatment of Anxiety Disorders in Children and Adolescents

Özgür Yorbik, Boris Birmaher

INTRODUCTION

Anxiety disorders are among the most common of childhood psychiatric disorders, which may be associated with low self-esteem, substance abuse, depression, social isolation, inadequate social skills, and academic difficulties. The aim of the presented article is to review the drug treatment of anxiety disorders. Selected papers and books regarding to drug treatment of anxiety disorders were reviewed. Currently the selective serotonin receptor inhibitors are the first choice for the short-term treatment of anxiety disorders in children and adolescent, because they have been shown to be effective and safe. It is recommended to begin the treatment with very low doses and increase gradually to avoid side effects and compromise the adherence to treatment. The medication should be administered at therapeutic dosages for at least 6 weeks to decide effectiveness of the treatment. The studies on drug treatment of anxiety disorders in children and adolescent are scarce. More well designed, double blind, placebo controlled studies on drug treatment of anxiety disorder are required.

Key words: anxiety disorders, drug therapy, children, adolescent

Pharmacological treatment of anxiety disorders in children and adolescents

Table 1. Pharmacological Studies in Children and Adolescent with Separation Anxiety Disorder, Social Phobia, and Generalized Anxiety Disorder.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study</th>
<th>n</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
<th>Results (effectivity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berney et al (1981)</td>
<td>Double-blinded and placebo controlled,</td>
<td>51</td>
<td>9-14</td>
<td>SR</td>
<td>Clomipramine</td>
<td>40-75 mg/day</td>
<td>12 weeks</td>
<td>Clomipramine = placebo</td>
</tr>
<tr>
<td>Simeon and Ferguson (1987)</td>
<td>Open-label Placebo-drug-placebo crossover,</td>
<td>12</td>
<td>8.8-16.5</td>
<td>OAD</td>
<td>Alprazolam</td>
<td>0.5-1.5 mg/day</td>
<td>4 weeks</td>
<td>Alprazolam &gt; placebo</td>
</tr>
<tr>
<td>Bernstein et al (1990)</td>
<td>Double-blinded and placebo controlled,</td>
<td>24</td>
<td>7-18</td>
<td>SR with DD or ANXD</td>
<td>Imipramine</td>
<td>3 mg/kg/d for imipramine; 0.03 mg/kg/d for alprazolam</td>
<td>8 week</td>
<td>Medications = placebo.</td>
</tr>
<tr>
<td>Simeon and Ferguson (1992)</td>
<td>Double-blinded and placebo controlled,</td>
<td>30</td>
<td>8-17</td>
<td>OAD, AVD</td>
<td>Alprazolam</td>
<td>0.5-3.5 mg/day</td>
<td>4 weeks</td>
<td>Alprazolam = placebo</td>
</tr>
<tr>
<td>Klein et al (1992)</td>
<td>Double-blinded and placebo controlled,</td>
<td>20</td>
<td>6-15</td>
<td>SAD</td>
<td>Imipramine</td>
<td>5 mg/kg/day</td>
<td>6 weeks</td>
<td>Imipramine = placebo</td>
</tr>
<tr>
<td>Graae et al (1994)</td>
<td>Double-blinded and placebo controlled,</td>
<td>15</td>
<td>7-13</td>
<td>SAD</td>
<td>Clonazepam</td>
<td>Up to 2mg/day</td>
<td>4 weeks</td>
<td>Clonazepam = placebo, side effects observed frequent.</td>
</tr>
<tr>
<td>Black and Uhde (1994)</td>
<td>Double-blinded and placebo controlled,</td>
<td>15</td>
<td>6-11</td>
<td>SM, SP, AVD</td>
<td>Fluoxetine</td>
<td>0.6 mg/kg/day</td>
<td>12 weeks</td>
<td>Effective (on parents’ rating) and safe</td>
</tr>
<tr>
<td>Birmaher et al (1994)</td>
<td>Open,</td>
<td>21</td>
<td>11-17</td>
<td>OAD, SP, SAD</td>
<td>Fluoxetine</td>
<td>10-60 mg/day/months</td>
<td>Up to 10</td>
<td>Effective and safe</td>
</tr>
<tr>
<td>Dummit et al (1996)</td>
<td>Open,</td>
<td>21</td>
<td>5-14</td>
<td>SM</td>
<td>Fluoxetine</td>
<td>10-60 mg/day</td>
<td>9 week</td>
<td>Effective, 3 patients discontinued fluoxetine because of disinhibition</td>
</tr>
<tr>
<td>Fairbanks et al (1997)</td>
<td>Open,</td>
<td>16</td>
<td>9-18</td>
<td>SP, GAD, SAD, SPP, PD</td>
<td>Fluoxetine</td>
<td>Up to 40 mg/day (children under ) 12 Up to 80 mg/day (adolescent)</td>
<td>6-9 weeks</td>
<td>Effective, and safe</td>
</tr>
<tr>
<td>Bernstein et al (2000)</td>
<td>Double-blinded and placebo controlled,</td>
<td>63</td>
<td>13.9 ± 3.6</td>
<td>SR with DD or ANXD</td>
<td>Imipramine</td>
<td>3 mg/kg/d</td>
<td>8 weeks</td>
<td>Imipramine + CBT &gt; Placebo + CBT</td>
</tr>
<tr>
<td>Rynn et al (2001)</td>
<td>Placebo-controlled,</td>
<td>22</td>
<td>5-17</td>
<td>GAD</td>
<td>Sertraline</td>
<td>50 mg/day</td>
<td>9 weeks</td>
<td>Effective and safe</td>
</tr>
<tr>
<td>Compton et al (2001)</td>
<td>Open,</td>
<td>14</td>
<td>10-17</td>
<td>SP</td>
<td>Sertraline</td>
<td>Mean: 123.21 ± 37.29 mg/day</td>
<td>8 weeks</td>
<td>Effective and safe</td>
</tr>
<tr>
<td>RUPP (2001)</td>
<td>Placebo-controlled,</td>
<td>128</td>
<td>6-17</td>
<td>GAD, SP, SAD</td>
<td>Fluvoxamine</td>
<td>Up to 300 mg/day</td>
<td>8 weeks</td>
<td>Effective, 8% discontinued fluvoxamine because of adverse effects</td>
</tr>
<tr>
<td>Khan et al (2002)</td>
<td>Double-blinded and placebo controlled,</td>
<td>156</td>
<td>6-17</td>
<td>GAD</td>
<td>Venlafaxine XR</td>
<td>Up to 225 mg/day</td>
<td>≤ 8 weeks</td>
<td>Venlafaxine XR &gt; placebo</td>
</tr>
</tbody>
</table>

Legend: OAD: Overanxious disorder; SP: Social Phobia; SAD: Separation Anxiety Disorder; AVD: Avoidant Disorder; SM: Selective Mutism; SR: School Refuser; DD: Depressive Disorder; ANXD: Anxiety Disorder; SPP: Specific Phobia; PD: Panic Disorder; GAD: Generalize Anxiety Disorder
may be easily misinterpreted as side effects of future pharmacological treatment. Multiple informants and several sessions with the child and their parents are useful to obtain an adequate history and mental status examination. Information about premorbid functioning, substance abuse, onset of condition and developmental and psychiatric family history should be obtained.

Considering the age and developmental level of the child, a variety of rating scales may be used to gather information from patients, parents (about their children and themselves), teachers, and significant others (34). Medical history and examination should be done and laboratory should be tests requested if warranted. Since anxiety disorders in youth are often associated with high rates of comorbidity with other psychiatric disorders such as depression (9,35-37), these comorbid disorders should be diagnosed and treated appropriately. Hospitalization may be required for severe cases or if there is high risk for suicide. Since parents of anxious youth usually have psychiatric disorders, to improve the child’s prognosis it is recommended to refer them for the treatment as well.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

All the selective serotonin receptor inhibitors (SSRIs) are well absorbed from the gastrointestinal track after oral administration. Hematology and chemistry testing are usually not necessary before treatment with the SSRIs (38). The preliminary reports suggest that SSRIs are efficacious for the treatment of anxiety disorders in children and adolescents (Table 1) (39-45). The time course of improvement with the SSRIs for anxiety disorders is approximately 4 to 6 weeks. The dosages of the SSRIs are similar to the ones used to treat depression (Table 2), but the length of treatment needed to avoid relapses or recurrences has not been determined yet (43,46).

### Fluoxetine:

Fluoxetine has a long half-life (1 to 4 days) in adults compared with other SSRIs. Norfluoxetine, the primary metabolite of fluoxetine, is at least as potent inhibitor of serotonin as its parental compound, fluoxetine, and it has a long half-life of approximately 7 to 15 days in adults (47,48). Fluoxetine inhibits its own metabolism; its half-life gets longer with increased dosage, and its plasma concentration increases disproportionately (49). Because of these facts, when treating a patient with fluoxetine, it is reasonable to wait at least 4 to 6 weeks before increasing the dose. The usual dosage is 20 mg/day, but some patients may respond to lower dosages (e.g., 5 mg/day). Maximum dosages up to 60 mg/day are sometimes necessary (46).

To date, three open label studies and one double blind and placebo-controlled study of fluoxetine in youth with anxiety disorders have been reported. Open label studies suggested that fluoxetine is efficient for the treatment of children with overanxious disorder (OAD), SP, SAD, and SM (39,41,42). A double blind and placebo-controlled study of fluoxetine (20 mg/day) in 15 children (mean age: 8.5±1.9 years) with SM and SP showed that fluoxetine was significantly better than placebo and well tolerated (50). Recently a double blind randomized controlled trial compared a fixed dose of fluoxetine (20 mg/day) to placebo for the treatment of 74 children and adolescents with SP, GAD, and/or SAD. Approximately 60% of the patients treated with fluoxetine showed much to very much improvement in comparison with 30% of those randomized to placebo (Birmaher et al, personal communication).

### Sertraline:

The half-life of sertraline, the parent compound, has been reported to be about 1 day in adult, and 14 hours in youth (Axelson et al, in press). Desmethylsertraline, the principal metabolite of sertraline, has longer half-life, but it is not pharmacologically active. Sertraline exhibits a linear relationship between dose and plasma concentration (49,51). In general, treatment is initiated at 25 mg/day with a target dose of 50 mg day to 200 mg/day (46). Rynn et al (2001) examined the safety and efficacy of a fixed dose of sertraline (50 mg/day) treatment compared to the placebo for 22 children and adolescents aged 5-17 years with GAD (44). Ten of the 11 patients who received sertraline (90%), but only one of the 11 who received placebo (10%) improved. However, of those patients who improved
while taking sertraline, only two patients were markedly improved, representing a possible remission rate of only 18%. Overall, sertraline was well.

An open label trial of sertraline (mean dose 123.21+/−37.29 mg per day) in 14 children with social anxiety disorder showed that sertraline resulted in significant improvement in symptoms of childhood social anxiety disorder. Sertraline was generally well tolerated (52).

**Fluvoxamine:**

In adults, the half-life of the fluvoxamine is about 12 to 24 hours (53) and has no active metabolites (51). Fluvoxamine displays a linear relationship between dose and plasma concentration. Fluvoxamine is usually started at 25 mg/day with a target dose of 50 mg/day to 200 mg/day (46).

Recently, the RUPP Anxiety Study Group (2001) compared the effects of a flexible dose of fluvoxamine and placebo in a group of 128 children and adolescent (aged 6 to 17) with SP, SAD, or GAD (45). The dose of fluvoxamine was increased by approximately 50 mg per week to a maximum of 300 mg per day in adolescents and 250 mg per day in children less than 12 years of age with a mean group dose of 150 mg/day by the end of the study. Approximately 70% of the anxious youth treated with fluvoxamine and 30% of those receiving placebo showed moderate to very strong response. Five children in the fluvoxamine group (8 percent) discontinued treatment because of adverse events, as compared with one child (2 percent) in the placebo group.

**Side effects of the SSRIs:**

The SSRIs’ studies in children and adolescent with anxiety disorders suggested that the side effects of SSRIs are usually mild and transient. They present the advantage of having fewer anticholinergic and antihistaminic side effects, and lack of serious systemic toxicity in relatively high doses (38). One of the great concerns about SSRIs, like other antidepressants is that they may activate hypomania or mania especially in the youth with a family history of affective disorders. Children and adolescents receiving SSRI therapy should be monitored for the development of hypomanic and manic symptoms. Although previous reports suggesting that SSRIs use is associated with increased suicidal risk (54), Khan and colleagues reported that there is no difference in suicide risk between SSRIs and placebo (55). The common side effects reported in association with SSRIs include gastrointestinal difficulties (abdominal discomfort, nausea, diarrhea, vomiting, and decreased appetite), central nervous system (CNS) effects (increased motor activity, agitation, disinhibition that is so-called behavioral activation, headache, and insomnia). The other side effects of SSRIs includes decreased appetite and weight, abdominal pain, drowsiness, tremor, restlessness, hypersomnia, increased diaphoresis, delayed ejaculation, anorgasmia, vivid dreams, apathy, seizures, akathisia, ecchymoses, hyponatremia, and allergies. In addition, the serotonin syndrome may occur when SSRIs are combined with MAOs. This syndrome carries the potential for significant morbidity and mortality; it is characterized by symptoms such as confusion, myoclonus, hyperreflexia, diaphoresis, and possibly cardiovascular compromise (56).

SSRIs like other antidepressants and benzodiazepines may cause agitation or disinhibition. Referred to as a loss of the ability to control one’s impulses, disinhibition may result in nonspecific behavioral activation including giddiness, agitation, confusion, irritability, insomnia, temper outburst, anxiety, or aggression. Disinhibiton generally occurs immediately after the initial exposure (<30 minutes) to a medication and dissipates commensurate with the plasma half-life of the medication. The disinhibition caused by the SSRIs needs to be differentiated from mania/hypomania induced by these medications (57).

**Tricyclic antidepressants:**

Absorption from oral administration of most tricyclic antidepressants (TCAs) is incomplete, and the pharmacokinetics of TCAs are characterized by substantial presystemic first-pass metabolism, a large volume of distribution, extensive protein binding, and an elimination half-life averaging about 1 day (up to 3 days for protriptyline) (58).

The reports regarding the use of the TCAs for the treatment of children and adolescent with anxiety disorders are conflicting (Table 1). Moreover most of the reported studies have included children with school refusal whom not necessarily had anxiety disorders. In a 6-week double-blind controlled study of 35 children, aged 6 to 14 years, with anxiety-based school refusal, imipramine was found to be significantly superior to placebo (59). However, Klein et al did not replicate this finding in a group of 21 children with separation-anxiety (60). Bernstein et al, in a double blind controlled study also did not find statistically significant differences among imipramine,
alprazolam and placebo in a small sample (n=24) of school refusers, aged 7 to 18 years, with depression or anxiety disorders (61). Recently, Bernstein and colleagues in a 8-weeks double blind-placebo controlled study comparing imipramine plus CBT versus placebo plus CBT alone found that imipramine plus CBT was better in improving school attendance and decreasing symptoms of depression in 65 school-refusing adolescent with comorbid anxiety and depression (62). Berney et al, in a 12-weeks double blind placebo-controlled study, found no significant differences between placebo and clomipramine in decreasing symptomatology or facilitating in a return to school in 51 school refusers, ages 9 to 14 years old (63). The inconsistent reports noted above may be accounted by the differences in sample sizes, presence or absence of comorbid disorders, dosages, and type and control of concurrent therapies (25).

Side effects of TCAs:

Numerous of the TCAs side effects are reasoned by blockade of cholinergic, histaminic, and adrenergic receptors. TCAs have “quinidine-like” effect on cardiovascular system, which may result in slower intracardiac conduction and increased heart rate, flattened T waves, prolonged QT intervals, and depressed ST segments on electrocardiograms (EKGs) (56, 64). A number of case reports proposed the sudden unexplained death occurring in children stable on TCA medications (65-68). At least two of them due to imipramine and desipramine metabolite accumulation which has been shown by a postmortem study (69). Impaired metabolism was caused by a genetically determined “slow metabolizer” phenotype of cytochrome CYP2D6, and/or concurrent therapy with phenothiazines in these cases, which warrants physicians to treat all patients as if they were poor metabolizers for the drugs, especially in combined pharmochotherapy (69). It would be helpful to predict which patients are at greater risk for the development of serious adverse effects to TCAs. Potential factors include pre-existing abnormalities in the ECG, such as a bundle branch block or other conduction problem, a prior history of cardiac arrhythmia and a family history of early onset cardiac disease. It appears appropriate to show special concern in the presence of these factors, but it is not currently clear whether these factors convey an additive risk to the development of catastrophic cardiovascular adverse effects (70). Varley offers following proposal: (i) initial utilization of alternative agents, with TCAs as secondary or tertiary agents; (ii) informed consent/assent by the patient and family which should include mention of the reports of sudden death and discussion of the controversy as to the relationship of TCAs, if any, to sudden deaths; (iii) vigilance regarding the emerging literature; (iv) systematic ECGs, serum concentrations and vital sign monitoring (Table 3). Blood levels should be obtained 10 to 12 hours after the last oral dose (46).

**Table 3. An Example of a Tricyclic Antidepressant Protocol (70)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obtain baseline ECG to assess for pre-existing arrhythmias or cardiac conduction delays</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Begin TCA treatment at</strong></td>
<td>1 mg/kg/day (0.5 mg/kg/day for nortriptiline)</td>
</tr>
<tr>
<td><strong>Advance dose no more rapidly than every 5 days.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Repeat ECG at 3.0 mg/kg/day and at any subsequent dose increases with the following parameters</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PR interval &lt;0.18 sec in children &lt;10 years</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PR interval &lt;0.2 sec in children &gt;10 years</strong></td>
<td></td>
</tr>
<tr>
<td><strong>QRS complex &lt;0.12 sec</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Corrected QT interval &lt;0.45 sec</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Vital signs monitoring:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline postural pulse and blood pressure</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Regular monitoring of postural pulse and blood pressure</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Obtain serum concentrations after steady state if TCA dosage &lt;3mg/kg/day</strong></td>
<td></td>
</tr>
<tr>
<td><strong>If dosage exceeds 3 mg/kg/day, obtain serum concentration at 3 mg/kg/day, and at ceiling dose. Serum concentration should not exceed 500 mg/L.</strong></td>
<td></td>
</tr>
</tbody>
</table>

TCA seems more likely to induce manifform states (mania or hypomania) than SSRIs (71,72). Other side effects of TCA include anticholinergic side effects like dry mouth, constipation, blurred vision, urinary retention; sedation due to serotoninergic, cholinergic, and histaminergic activities; weight gain reasoned by histamine H1 receptors; autonomic side effects partly because of alpha-1 adrenergic blockade like orthostatic hypotension; delirium possibly reasoned by anticholinergic effects; seizures, myoclonus, dizziness, cognitive disturbance, agnulositosis, leukositosis, leukopenia, eosinophilia, hyperprolactinemia, galactorrhea, anorgasmia, ejaculatory disturbances, inappropriate secretion of antidiuretic hormone, nausea, vomiting, hepatitis, skin rashes, speech blockage, paresthesia, peroneal palsies, and ataxia (46,56,73,74). As a consequence of anticolinergic activities, TCA aggravate the precipitation of glaucoma requires emergency treatment with a miotic agent. TCA should not be administered during a course of electroconvulsive therapy, primarily because of the risk of serious adverse cardiac effects.

**Benzodiazepines**

The benzodiazepines are usually used as anxiolytics, hypnotics, anticonvulsants, and muscle
Side effects of benzodiazepines:

As in adults, sedation is the most common side effect observed in children. This side effect is dose-related and generally resolve as tolerance develops (81,82). Other side effects include irritability, agitation, nausea, constipation, dry mouth, dizziness, headache, blurred vision, abdominal pain, disinhibition, and tiredness. No data have been published regarding the risk of physiological and psychological dependence in children and adolescents. However, it is recommended that benzodiazepines be prescribed for youth for only short periods of time (i.e., weeks rather than months) because of the theoretical potential for dependence (81). It is also recommended that benzodiazepines should be used as adjunctive to other treatments.

Other Pharmacological treatments

Recently a double blind randomized controlled trial compared a flexible-dose of venlafaxine XR (37.5-225 mg/day) to placebo for the treatment of 156 children and adolescents with GAD. Response rates were significantly higher in the venlafaxine XR group (64%) than in the placebo group (40%). Venlafaxine was found to be effective and well-tolerated treatment for children and adolescent with GAD. The most common adverse effects of venlafaxine XR were asthenia, anorexia, weight loss, hyperkinesia, and epistaxis (83). The other adverse reactions of venlafaxine in adults were sweating, nausea, constipation, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, blurred vision, hypertension, abnormal ejaculation or orgasm, and impotence. In addition, a venlafaxine withdrawal syndrome involving mainly gastrointestinal and CNS symptoms was described. The drug should be gradually tapered over 2 to 4 weeks and over a longer period when required (56). Further studies are needed to show reliability of venlafaxine for the treatment of anxiety disorders in youth.

Although no studies using paroxetine, citalopram, bupropion, nefazodone, MAOIs, buspirone, and beta-blockers, have been reported in youth, these compounds have been found for the treatment of the anxious adults (46,84-87).

Hydroxyzine, an antihistaminic medication, was found to be effective compared to the placebo in a small study for adults with anxiety disorder (88-90), but no studies has been done in children with anxiety disorders. Antihistamines may induce drowsiness, agitation, and cognitive and affective side effectes (46,91).

CONCLUSIONS

Currently the SSRIs are the first choice for the short term treatment of anxiety disorders in children, because they have been shown to be effective and safe. However, other medications, such as the benzodiazepines, may be used alone or sometimes in combination with SSRIs.

Children, compared to adults, have greater hepatic capacity, more glomerular filtration, and less fatty tissue. Therefore children eliminate many psychotropic drugs more rapidly than adults. Because of children's quick elimination, the half-lives of many medications may be shorter in children than adults (56). It is recommended to begin the treatment with very low doses and increase gradually to avoid side effects and compromise the adherence to treatment. The medication should be administered at therapeutic dosages for least 6 weeks to decide effectiveness of the treatment. Since fluoxetine has a longer half-life, titration may require a longer trial period. The discontinuation of the medication should be slow (e.g. for at least 4 to 6 weeks) to avoid withdrawal adverse effects. When several medications are administered, drug interactions should be kept in mind, and lower doses should be considered if the
medications used interact with the same cytochrome P450 coenzyme system. The duration of drug therapy in youth with anxiety disorder has not been ascertained yet and continuation and maintenance studies are warranted. More well designed, double blind, placebo controlled studies on youth are required. Studies are also needed to test and compare the effects of antidepressants versus CBT, the only type of psychotherapy that has been shown in randomized controlled trials to be effective for the acute and continuation treatment of youth with anxiety disorders.

References:


