Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines

Geneva, 29 September to 3 October 2008

WHO essential drugs for common Psychiatric disorders in children.

1. Anxiety disorders-
2. Depression
3. Bipolar disorder
4. Attention Deficit Hyperactivity disorder
4. Tourette's syndrome
5. Enuresis
6. Psychotic disorders

1. Anxiety disorders:

SSRIs are the medications of choice in treating childhood anxiety disorders. They are well tolerated with mild transient side effects. Controlled trials have established the safety and efficacy of SSRI's for childhood anxiety disorders. Fluoxetine, Fluvoxamine and Sertraline have been shown to be more effective than Placebo in RCT's. As anxiety disorders often co-exist with depression, children prescribed SSRI's for both conditions should be monitored closely for increased suicidal thoughts and behaviour. Since SSRI's have been available, TCA's are used less often because of the need for cardiac monitoring and the medical risks associated with overdose of TCA's. Venlafaxine, TCA's, and benzodiazepines may be used as alternatives to SSRIs. Benzodiazepines are used clinically as adjunct short term treatment (2-4 weeks) with SSRIs for rapid reduction of severe symptoms of anxiety.

Recommend for essential drug list: Fluoxetine; Sertraline and/or Fluvoxamine

Fluoxetine: Liquid 20mg/5ml and capsules 20mg
Doses: 8-12 Years: start on 10mg/day; increase to 20 mgs after a few weeks if no therapeutic effect.

Sertraline Tablets:
Doses: 6-12 years; 25mgs single daily dose (morning or evening)
Increase by 25 mgs weekly if no therapeutic effect obtained. May be given in divided doses over 50mgs daily. Maximum dose 200mgs/day

Fluvoxamine: Tablets 50mg, 100mg
Doses: 8-12 years: 25mgs nocte; increase to 50mgs after a week if no effect.

Sources

AACAP Practice parameters for the Assessment and treatment of children and adolescents With Anxiety disorders. J Am Acad Child Adolescent Psych. 2007; 46(2):267-283

Black and Uhde TW (19940 Treatment of elective mutism with fluoxetine: a double blind, placebo controlled study. J Am Acad child Adolescent Psych. 33:1000-1006

Birmaher et al (2003) Fluoxetine for the treatment of childhood anxiety disorders (rdb study) J Am Acad Child Adolesc Psychiatry 42:415-423

Gittleman-Klein and Klein (1971) controlled Imipramine treatment of school phobia. Archives General Psychiatry 25:204-207

Research Units on Paediatric Psychopharmacology (RUPP) Anxiety Study Group, (2001) Fluvoxamine for the the treatment of anxiety disorders in children and adolescents. New England Journal of Medicine 344:1279-1285

Rynn MA, Siqueland L, Rickels K (2001) Placebo controlled trial of Sertralline in the treatment of children with Generalised anxiety disorders. American Journal of Psychiatry 158:2008-2014

Vitiello B. a multi site double blind placebo controlled trial of Fluvoxamine for children and adolescents with anxiety disorders. J child adolescent psychopharmacology. 2000:10:257-258 (abstract)

2. Depression

SSRIs: Fluoxetine is the only medication which has proven efficacy in clinical trials for treating depressive illness in children and adolescents. Other SSRI's have shown small differences between the drug and placebo. **Caution**: SSRI's are associated with an increased risk of suicidal thoughts and behaviour in the early phases of treatment. There have been no reports of completed suicides attributed to treatment with SSRI's. Children need careful monitoring with regular reviews during the early phases of treatment. Overall the use of SSRI's has decreased suicide rates in children and adolescents.

Recommend: Fluoxetine (liquid and capsules)
Dose: 8-12 years: initial dose 10mgs mane, increase to 20mgs mane after 2 weeks if necessary.

Sources

Bridge JA, Iyengar S, Salary CB et al (2007) clinical Response and risk for reported suicidal ideation and suicide attempts in paediatric antidepressant treatment: a Meta analysis of randomized controlled trials. JAMA 297: 1683-1696

Cheung AH, Emslie GJ, Mayes TL (2005) Review of the efficacy and safety of antidepressants in youth depression. J child psychol Psychiatry 46; 735-754

Emslie GJ, Rush AJ, Weinberg WA et al (19970. A double blind, randomized, placebo controlled trial of Fluoxetine in children and adolescents with depression. Arch Gene psychiatry 54: 1031-1037

Hammad T, Laughren T, Racoosin J. Suicidality in paediatric patients treated with antidepressant drugs. Arch Gen Psych 2006; 63:332-339

Hazell P, O'Connell D, Heathcote D, Hebry D (2006)Tricyclic drugs for depression in children and adolescents. Cochrane Depression, Anxiety, Anxiety and neurosis group. Cochrane Database syst Rev

NICE guidelines: Depression in children and young people. October, 2005.

3. Bipolar disorder:

The validity of Bipolar disorder in young children has not yet been established. In the USA the number of children diagnosed with BD has been increasing in the past decade; this is not a global trend. There is ongoing debate and controversy on BD as a diagnosis in children, therefore no global consensus on treatment. Treatment guidelines are based on adult literature. In the USA only Lithium is FDA approved for use in children over 12years.My opinion is that it is premature to include any medications for children in this category.

4. Attention Deficit Hyperactivity disorder.

Efficacy of **stimulants** in treating childhood ADHD has been demonstrated in many double blind, placebo-controlled trials during the past 3 decades. Two types of stimulants- **Methylphenidate and amphetamine**-have equal efficacy. Both are available in short and long acting preparations. Short acting immediate release formulations must be taken 2 or 3 times during the day. Longer acting sustained release formulations have equal efficacy, are more convenient and enhance compliance as they are given by the parents as a single daily dose. Short acting formulations are useful in initiating treatment in children under 16Kgs in weight; sustained release medications are not available in very low doses but are increasingly used as first line treatment in older children. Medication is not recommended for children younger than 6years old.

i) Methylphenidate: (first line)

Short acting (e.g. Ritalin)
Modified release/sustained release (e.g. Concerta, Equasym XL, Ritalin LA). Some children have difficulty swallowing capsules which have to be swallowed whole (Concerta). Ritalin LA and Equasym XL capsules may be opened, sprinkled on soft food and swallowed without chewing.

Ritalin: Formulation: Tablets Available as 5mg, 10mg (scored), 20mg (scored)
Doses: 4-6 years: 2.5mgs twice a day; increase weekly by 2.5mgs if needed
Maximum dose: 1.4mgs/Kg/Day in divided doses

6-12 years: 5mgs once or twice a day; increase by 5 mgs weekly if needed;
Maximum dose 60mgs/day

Concerta XL: Formulation Capsules Available as 18mgs, 27mgs. 36mgs, 54mgs:
Doses: 6-18 years: 18mgs mane; increase by 18mgs weekly if needed
Maximum dose 54mgs

Equasym XL: Formulation Available as 10mg, 20mg, 30mg Capsules
Doses: 6-18 years: 10mgs mane; increase by 10mgs weekly if needed.
Maximum dose 60mgs daily

Due to concerns about the long term effects of stimulants on growth it is recommended that a child's height and weight should be monitored at least once or twice a year on growth charts (more frequently if needed). If the child fails to maintain expected growth consider a drug holiday or a different medication and check for growth recovery.

ii) Atomoxetine (Selective norepinephrine reuptake inhibitor). Prescribed as a second line medication if child has severe side effects on stimulants, or if stimulants are contra indicated. Atomoxetine has a delayed onset of action and may take several weeks to observe therapeutic effect. Parents and children often prefer the option of taking drug breaks on weekends or during school holidays; Atomoxetine must be taken continuously which makes it less desirable for some families.

Formulation: Capsules: 10mg, 18mg, 25mg, 40mg, 60mg
Dose: 6-12 years: initial dose 0.5mgs/Kg/day as a single daily dose morning or evening; after one week increase to maintenance dose of 1.2mgs/Kg/day as a single daily dose or divided doses twice a day.
Maximum dose: 1.4 mg/Kg/day

iii) Amphetamine preparations: Used primarily for refractory ADHD.
Short acting e.g. Aderall, Dexedrine (5mgs scored tablet),
Long acting e.g. Aderall XR

Doses: 6-12 years: start with 2.5 mgs twice a day; increase weekly by 2.5-5mgs. Maximum dose is 20mgs daily in divided doses.

Caution: ADHD often co-exists with Tourettes and epilepsy. Children on stimulants who also have Tourettes or Epilepsy should be monitored closely to ensure that ADHD medication does not exacerbate the condition. Amphetamines have greater tendency for exacerbation than methylphenidate. Amphetamines have a high potential for abuse. Use for prolonged periods of time may lead to drug dependence

Recommendation for essential drug list: Methylphenidate (short acting and modified/ sustained release preparations). Atomoxetine (supplementary list)

Sources

American Academy of child and Adolescent Psychiatry (AACAP): practice parameters for the assessment and treatment of children and Adolescents with ADHD. J. Am Acad. Child Adolesc Psych, 2007; 46(7):894-921

Arnold LE et al: a double blind, placebo controlled withdrawal trial of dexmethylphenidate hydrochloride in children with ADHD. J child Adolesc Psychopharmacology 2004; 14:542-554

Greenhill LL, Kollins S, Abikoff H et al Efficacy and safety of immediate release methylphenidate treatment for preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry 45:1284-1293

Greenhill LL, Muniz R, Ball RR, Levine A, Pestreich l, Jiang H (2006b) Efficacy and safety of Dexmethylphenidate extended release capsules in children with ADHD. J Am Acad child Adolesc Psychiatry 45; 817-823

Kemner JE et al. Outcomes of OROs methylphenidate compared with Atomoxetine in children with ADHD: a multi centre, randomized prospective study. Advances in therapy 2005; 22:498-512

Michelson D< Allen AJ, Busner J et al (2002). Once daily Atomoxetine treatment for children and adolescents with ADHD: a randomised, placebo controlled study. Am J psychiatry 159: 1896-1901.

MTA cooperative Group(2004a) National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24 month outcomes of treatment strategies for ADHD. Paediatrics 113: 754-761

National Institute for clinical excellence (NICE) guidelines: ADHD treatment review (Methylphenidate, Atomoxetine, and dexamphetamine). March, 2006.

4. Tourettes syndrome (classified as a neurological disorder)

Medications with proven efficacy for treating touretts syndrome in children:
Clonidine, haloperidol, pimozide, risperidone, sulpiride. (See note on antipsychotics under 6 below).

Haloperidol: Formulation: tablets and oral concentrate (2mg/ml)
Dose: 3-12 years (15-40 Kgs) start with 0.5mgs daily increase by 0.5mgs weekly.
Therapeutic dose range; 0.05-0.075mh/kg/day

Sulpiride: 2-12 years 50-400mgs in divided doses

Clonidine(second line for children who have not responded to standard treatment)
May cause hypertensive reaction and other withdrawal symptoms if withdrawn rapidly

Pimozide: tablets 1mg,2mg
2-12 years initial dose 0.05mg/kg/day at night; increase every third day to maximum dose of 0.2mg/kg/day (not to exceed 10mg/day)

Recommend: Pimozide and Haloperidol

Shapiro AK, Shapiro E. Treatment of Guilles de la tourett syndrome with pimozide. Am J. Psychiatry 1983; 140:1183-1186

Sallee FR, Nesbitt L, Jackson C, Sine L, Sethuraman G. Relative efficacy of Haloperidol and Pimozide in children and Adolescents with tourette's disorder. Am J Psychiatry 1997; 154; 1057-1062 (1987)

5. Enuresis

Imipramine has been used extensively for treating primary nocturnal enuresis. It is important to first exclude possible organic causes for enuresis. Imipramine is effective in doses lower than when it is used as an anti-depressant. There is a high relapse rate when the drug is discontinued.

6-11years: Usual dose is 1-2.5mg/Kg in a single dose at night. Start with 25mgs at night, increase to 50mgs after one week if no response. Maximum dose is 2.5mg/Kg/day or 50mgs/day. **Caution**: Cardiac Disease, epilepsy. An ECG is recommended before starting medication.

DDAVP: nasal spray and tablets

AACAP Practice parameters for the Assessment and treatment of Children and Adolescents with Enuresis. J.Am. Acad. Child Adolesc. Psychiatry, 2004; 43(12):1540 1550.

Mark and frank (1995) Nocturnal enuresis> British Journal of Urology 75:427-434

Moffat M (1997) Nocturnal Enuresis: a review of efficacy of treatment. J Dev Beh Paediatrics 18:49-56

6. Psychosis

Psychotic disorders are very rare in childhood. When psychotic symptoms occur the focus is to investigate and exclude underlying organic causes. There is limited information on the efficacy and safety of anti-psychotics in children for treating psychotic disorders. The trend is towards the use of atypical agents (e.g. sulperide, risperidone) which are less likely to cause extra pyramidal side effects. However there is increasing concern about the metabolic side effects of atypical antipsychotic (weight gain and developing type 2 diabetes). Although used in children none of the atypical antipsychotics are currently licensed for use in children less than 12 years for treating psychosis. As more data empirical data becomes available WHO will need to review the list and possibly include an atypical agent.

Haloperidol: formulation-tablets and oral liquid (already on WHO list)
Indications: acute and chronic psychotic disorders; Tourette's disorder
Doses: 3-12 years (15-40Kgs) Initial dose 0.5mgs daily; increase by 0.5mgs weekly. Maximum dose is 0.15mg/Kg/day

Chlorpromazine: although currently on the WHO List largactil is not used preferentially in clinical practice and may be replaced by atypical agents as more data becomes available on their use.

Recommend: remove Haloperidol and Chlorpromazine injections from list; keep oral liquid and tablets and review at later date.

Sources:

Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medication in children and adolescents. J Am Acad Child Adolesc 2006; 45:771-791

Patel NC, Crimson NL, Hoagwood K, Johnsrud MT, Rascati KL, Wilson JP, Jensen PS: Trends in the use of typical and atypical antipsychotics in children and adolescents. J Am Acad Child Adolescent Psychiatry 2005; 44:548-556

Other Sources:

British National Formulary for children, 2007.

Child and Adolescent Clinical psychopharmacology, fourth edition, Green W H., 2007

Summary of recommendations:

1. Generalised Anxiety disorder: (NB- OCD and panic attacks: classified under diagnostic category of anxiety disorders)
Fluoxetine (Capsules or Tablets and liquid 20mgs/5ml)
Capsules and tablets already on WHO list; add liquid formulation
Indications: Depression: Age restriction: USA (FDA)-not approved for use under 8years; UK not licensed for under 12 yrs
OCD: not FDA approved under 7years

Sertralline: Tablets
Indications: OCD: Age restriction; 6years
Fluvoxamine Tablets (supplementary list)
Indication: OCD; Age restriction 8years

Diazepam-already on list; may be used short term for reduction of severe symptoms of anxiety

2. Major Depression:
Fluoxetine: tablets and liquid as above.
Age restriction: FDA not approved less than 8 years
UK not licensed under 12years
Caution for SSRI's: Increased risk of suicidal thoughts in early phase of treatment therefore need close monitoring.

3. Bipolar disorder
No global consensus on diagnosis s and treatment in this age group

4. ADHD:
Methylphenidate immediate release: Tablets
Sustained release: tablets or capsules
Atomoxetine tablets (supplementary list)

5. Tourette's (classified as a neurological disorder)
Pimozide Tablets
Haloperidol (already on WHO list)

6. Enuresis (elimination disorder)
Imipramine tablets
DDAVP (supplementary list)

7. Psychotic disorders
Haloperidol and chlorpromazine-remove injection; keep tablets and oral liquid