Section 24: Medicines for mental and behavioral disorders

Request for Deletion of Haloperidol and Chlorpromazine from EMLc

Submitted by
Department of Mental Health and Substance Abuse (MSD)
World Health Organization, Geneva
Proposal for removing Haloperidol and Chlorpromazine from Model List of Essential Medicines for children (EMLc) for mental and behavioural disorders

*Department of Mental Health and Substance Abuse (MSD)*

WHO Essential medicines are selected by an international expert committee based on a set of criteria including disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness (1). In 2007, the World Health Assembly passed the Resolution ‘Better Medicines for Children’ which recognized among others the need for better dosage forms, better evidence and better information about medicines for treating the common childhood diseases. The World Health Organization has therefore developed a programme of work on medicines for children, including the development of a new Model List of Essential Medicines for children (EMLc). A 2nd List of Essential Medicines for Children, was recommended by the WHO Expert Committee on the Selection and Use of Essential Medicines in March 2009. In 2010, for the section 24. Medicines for Mental and Behavioural Disorders, the Committee noted “the potential importance of these medicines in children for a variety of disorders and requested a review of the entire section” (see annex 1).

The present discussion paper intends to provide a basis for discussing the issue of Medicines listed in EMLc under 24.1, Medicines used in Psychotic Disorders and whether we need to keep these medicines on the list before having reviewed the real needs of children for these medicines.

**Overview of the problem,**

**Magnitude**

Globally, about one fourth of children and adolescents experience a mental disorder during the previous year, and about one third across their lifetimes. Anxiety disorders are the most common condition, followed by behavior disorders, mood disorders and substance abuse disorders (2). Approximately 50% of all mental disorders in adults have an onset before the age of 14 years (3). According to a US national survey twelve-month prevalence estimates were anxiety, 18.1%; mood, 9.5%; impulse control, 8.9%; substance, 3.8%; and any disorder, 26.2% (4). Psychotic disorders are much less common and we shall elaborate further on this:

- **Psychosis in children,**

Psychosis is rare in childhood. There is no global data on the epidemiology as they are excluded from national surveys of children to prevent overestimation in lay-administered interviews (4). Some researchers have estimated it to be as low as 1.6/100,000 (5,6). However subclinical psychotic experiences (including delusions or hallucinations) are much more common. These more common conditions (6% in 11 year olds) are usually benign and in 75–90% cases spontaneously remit over time (7) and this should not be confused with a diagnosis of psychosis.
or schizophrenia in pre-pubertal children. Psychosis starts to become more prevalent after pubescence but the age ceiling for EMLc is 12 years which does not include them.

Services and Effective treatments

Children and adolescents in need of mental health services receive them less than adults. The median one-year treated prevalence for children and adolescents is 159 per 100,000 population compared to a treated prevalence of 664 per 100,000 for the adult population (8). According to ATLAS child mental health, the number of child psychiatrists ranges from 1 to 4 per million of the population in countries outside the north American and European region. More than half of the 67 countries participating in the ATLAS project identified pediatricians as the providers of mental health care while only 25% of the pediatricians in these countries were reported to have any mental health training and less than 10% of the care is provided in primary health care (3). The Lower treated prevalence of child mental disorders is more attributed to human resources limitations and not shortage of medicines. According to mental health Gap Action Programme- Intervention Guide (mhGAP-IG) evidence based recommendations with the exception of antiepileptics, and to a much smaller scale anti ADHD medicines, pharmacotherapy has a very limited role in the management of child mental disorders especially behavioural disorders before puberty. In the recently published evidence based mhGAP-IG a range of psychosocial interventions and not medicines have been recommended which are even applicable by non-specialized health care providers (9,10). Even for behavior disorders including ADHD in case of no response to first line psychosocial interventions, medicines might be considered only after careful review of the case and consultation with specialists. In any case antipsychotics have not been recommended to treat behavioural disorders of children (9,10). The mhGAP-IG evidence review strongly recommended the following (9):

“WHO does not recommend using pharmacotherapy for behavioural problems except for ADHD after a first trial with psychological interventions does not prove effective”.

Even in ADHD the second choice after psychological interventions is oral methylphenidate.

Inappropriate use of psychotropic medicines in children

Children’s vulnerability to domestic and school stressful events and maltreatments is high and translates into a wide range of clinical presentations that require a thoughtful holistic approach to either assessment and management. Their limited capacity to consent should also be taken into consideration. The limited capacity and skills of health providers in low and middle income countries and even some high income countries increases the chance of overmedicating children with psychotropic medicines. Though medicine use for children has been considered to be modest by some researchers in some high income countries such as USA(11,12); concerns about inappropriate use of psychotropic medicines in the same context, whether overuse or even underuse, have been raised (13, 14, 15). In some high income countries new to modern mental
health services more than 90% of children and adolescents who access specialist services receive prescriptions for their mental health conditions (16).

Safety of Haloperidol and Chlorpromazine for children

The international guideline development group (GDG) of mhGAP discouraged overuse of pharmacotherapy for mental disorders of children and adolescents and this was reflected in the recommendations and the final manual (9,10). Children are prone to a wide range of medicines side effects. Children seem to be more vulnerable to sedation, acute EPSs, withdrawal dyskinesia, hyperprolactinemia, and age-inappropriate weight gain with related metabolic abnormalities in general (11). Tardive dyskinesia may develop in children using antipsychotics (17,18). Injection of chlorpromazine is especially painful and may lead to serious local irritation (see the discussion under formulary below).

EMLc on Medicines used in psychotic disorders

According to the WHO Model List of Essential Medicines for Children 3rd list, March 2011, under 24.1, the list is a Complementary one and carrying an R to mention the need for revision. It includes chlorpromazine Injection: 25 mg (hydrochloride)/ml in 2 - ml ampoule. Oral liquid: 25 mg (hydrochloride)/5 ml. Tablet: 10 mg; 25 mg; 50 mg; 100 mg (hydrochloride) and Haloperidol Injection: 5 mg in 1 - ml ampoule. Oral liquid: 2 mg/ml. Solid oral dosage form: 0.5 mg; 2 mg; 5 mg.

The fact that it requires specialists for prescription is a positive aspect. But as we mentioned above and will further elaborate below the public health need for using these medicines in children under 12 is extremely low. This becomes more important given the WHO recent evidence based guidelines, taking into consideration the wide range of side effects which are more likely in children than adults, and the high possibility of off label use.

The current formulary on Haloperidol and Chlorpromazine in children

WHO Model Formulary for Children 2010 (19) elaborates fully and justifiably on precautions and the range of adverse effects but is very flexible about indication of use which goes beyond limitations of EMLc. For example it recommends use of antipsychotic drugs (neuroleptics) for behavioural problems and not only psychosis: “24.1 … In the short term, they are used to manage children with severe violent, threatening, aggressive or self-injurious behaviour that is not adequately controlled by other strategies…” For chlorpromazine it refers to a wide range of indications in addition to schizophrenia for example “… autism; psychomotor agitation and violent behaviour; adjunct in severe anxiety….”. Again we face the dilemma of off label use to control children’s behaviour.

Injections
FDA particularly highlights lack of controlled trials to establish the safety and effectiveness of intramuscular Haloperidol administration in children (20).

The formulary is detailed under chlorpromazine. For example under ATC code: N05AA01 Inction: 25 mg (as hydrochloride)/ml in 2 ml ampoule, oral liquid: 5 mg (as hydrochloride)/ml, tablet: 10 mg, 25 mg, 50 mg and 100 mg (hydrochloride) it emphasizes:

“Owing to the risk of contact sensitization, pharmacists, nurses and other health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care.” Italics are from present author.

Does it seem rational to consider injection of such a medicine to children under 12 even in disturbed psychotic state?

Discussion

We have reviewed the evidence regarding the rarity of genuine psychosis under 12, and the fact that according to recent WHO guidelines haloperidol and chlorpromazine are considered off label medicines for treating behavioural disorders of children. We have emphasized the importance of psychosocial interventions for children. We conclude that:

1. Psychosis is very rare in prepubescent children and psychotic experiences which are more common are transitory and self-remitting in the majority of cases.
2. The main consequence of keeping these two medicines on the list for children would be their application in managing behavioural problems of children which is considered as off label use by WHO.
3. We suggest to remove haloperidol and chlorpromazine from EMLc.

References:

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Annex

### 24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

The Committee noted the potential importance of these medicines in children for a variety of disorders and requests a review of the entire section.

24.1 Medicines used in psychotic disorders, Complementary List

**Chlorpromazine**

Injection: 25 mg (hydrochloride)/ml in 2-ml ampoule. Oral liquid: 25 mg (hydrochloride)/5 ml. Tablet: 10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).

**Haloperidol**

Injection: 5 mg in 1-ml ampoule. Oral liquid: 2 mg/ml. Solid oral dosage form: 0.5 mg; 2 mg; 5 mg.

### 24.2 Medicines used in mood disorders

24.2.1 Medicines used in depressive disorders, Complementary List

**Fluoxetine**

a Solid oral dosage form: 20 mg (as hydrochloride). a >8 years.

### 24.2.2 Medicines used in bipolar disorders

### 24.3 Medicines for anxiety disorders

### 24.4 Medicines used for obsessive compulsive disorders

### 24.5 Medicines for disorders due to psychoactive substance use