DRUGS USED IN THE TREATMENT OF CHILDHOOD PSYCHIATRIC DISORDERS

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Until recently, treatment of childhood psychiatric illness has been almost exclusively an art, rather than a science. Treatment methods, some extrapolated from work with adults and others developed specifically for youngsters, have been applied rather non-specifically, regardless of diagnosis. The choice of treatment method depended more on the training and theoretical beliefs of the therapist(1,2). A large clinical and scientific literature now bears witness to the difficulty of arriving at a rational policy of therapy(1).

The development of knowledge about drug treatment in children has been patchy. For some treatments–notably stimulant drugs for hyperkinesis–sophisticated research has led to clear information on their psychological actions. For other drugs such as benezodiazepines, this is not true. Firstly, in contrast to the extensive work on adult disorders, there is paucity of information in the pediatric psychopharmacology. Secondly, there is apprehension about the possible interference of these drugs with cognitive process and learning. Thirdly, the lack of knowledge about drug metabolism in children has meant that doses are unstandardized and treatment unreplicable. Lastly, the toxic manifestations of psychotropic drugs in children are different from those seen in adults, because of the differences in the rate of absorption, protein binding metabolism, and excretion.

Furthermore, psychotropic drugs are not usually a cure for a conditions but entail a complex package of actions on different aspects of behavior. An indication for therapy is then the presence of a target symptom, for which the cost of side effects is less than the expected benefit, and the drug treatment is either the more effective available therapy or a desirable adjunct to other treatments, such as psychotherapy, behavior therapy, *etc.*

The present review is an attempt to reveal the scope of drugs in the treatment of various childhood psychiatric problems. The important indications, benefits, adverse effects and recommendations of various drugs are given in *Table I* while *Table II* gives the average daily dosage. Important contraindications and special precautions of different categories of drugs are given in *Table III*.

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TABLE I—*Indications, Benefits, Adverse Effects and Recommendations of Various Drugs.*

Drug Group	Indications	Benefits	Adverse Effects	Recommendations
(I) Major tranquilizers	Infantile autism; pervasive development disorder; Tourette's syndrome conduct disorder, attention deficit disorder	Phenothiazines have potent sedative effect; butyrophenones are less sedating, have no anticholinergic effects and seizure threshold is not altered.	Extrapyramidal and anticholinergic effects; tardive dyskinesia on chronic intake; behavioral toxicity; weight gain	Start in lowest therapeutic doses with gradual increments not more than once or twice a week, use antiparkinsonain drugs whenever strongly indicated
(II) Minor tranquilizers	Anticipatory anxiety; avoidant and over-anxious disorder; sleep disorders	Low side effects profile	Sedation, ataxia, confusion, emotional lability, worsening of psychosis, dependence, paradoxical or disinheriting reactions	Start in lowest therapeutic doses and withdraw gradually
(III) Antidepressants	Depression; school avoidance or separation anxiety; enuresis; attention deficit disorder; sleep disorders; obsessive compulsive neurosis	Easily tolerated; single daily dose can be given as nortriptyline less sedating	Quinidine like effects, anticholinergic effects, behavioral toxicity, mania, allergic reactions, MAO inhibitors have dietary interactions with tyramine containing foods	Start in lowest doses with gradual increments or withdrawal, ECG monitoring, avoid tyramine, containing food items, *e.g.*, cheese chocolate, *etc.*
(IV) Stimulants	Attention deficit disorder with or without hyperactivity, sleep disorders (somnolence and somnambulsim); enuresis	Non-sedating drugs	Anorexia, weight loss, insomnia, abdominal pain, impaired cognitive performance, dependence psychosis, tics	Start in lowest therapeutic doses and gradually, avoid prolonged use.
(V) Anticonvulsants	Epilepsy; aggressive impulsive disorder; carbamazepine in manic depressive psychosis	Carbamazepine less sedating and has less behavioral toxicity	Carbamazepine causes nausea, vomiting, vertigo, diplopia nystagmus, tics, thyroid	Start in low therapeutic doses and withdraw gradually

				dysfunction. Phenobarbitone causes behavioral toxicity and dependence	
(VI)	Lithium carbonate	Bipolar effective disorders mixed or mania, aggression	Superior to major tranquilizers in controlling aggression, hostility and tantrums	Nausea, diarrhea, muscle cramps, thirst, polyuria hypothyroidism, weight gain	Assess renal, thyroid and cardiac functions before starting, start in lowest doses and monitor serum level, give after meals
(VII)	Central anticholinergics	Dystonic reactions, drug induced parkinsonism	They potentiate the sedative effects of major tranquilizers	Anticholinergic effects, mask tardive dyskinesia, psychosis lowers the serum levels of neuroletics	Use whenever strongly indicated

TABLE II—*Dosages of Drugs Used in Childhood Psychiatric Disorders*

Drugs	*Daily dose*
(A) Major tranquilizers	
1. *Phenothiazines*	
Chlorpromazine	1.5-5.0 mg/kg
Trifluoperazine	0.1-0.5 mg/kg
Thioridazine	1.5-5.0 mg/kg
2. *Butyrophenones*	
Haloperidol	0.25-1.0 mg/kg
Pimozine	0.04-0.08 mg/kg
(B) Minor tranquilizers	
Diazepam	5.0-20.0 mg
Chlordiazepoxide	5.0-20.0 mg
Flurazepam	7.5-15.0 mg
Nitrazepam	2.5-10.0 mg
Lorazepam	1.0-4.0 mg (divided doses)
Alprazolam	0.5-1.0 mg (divided doses)
(C) Antidepressants	
1. Tricyclics (Imipramine, Amitriptyline, Nortriptyline)	1.0-5.0 mg/kg
2. Tetracyclics Mianserin	0.2-1.0 mg/kg
3. Minoamine oxidase inhibitrs (not available in India) Phenelzine	2.0-5.0 mg/kg
4. Newer drugs Trazodone	1.0-5.0 mg/kg
(D) Stimulants (not available in India)	
Dextroamphetamine	0.3-0.5 mg/kg
Methylphenidate	0.5-1.5 mg/kg
Magnesium pemoline	0.5-3.0 mg/kg
(E) Anticonvulsants	
Phenytoin	4.0-7.0 mg/kg
Phenobarbitone	3.0-5.0 mg/kg
Carbamazepine	20.0-30.0 mg/kg
(F) Miscellaneous	
Lithium carbonate	Dose to maintain serum levels between 0.3-1.2 meq/L
Chloral derivatives	25-50 mg
Antihistaminics Diphenhydramine, promethazine	25-150 mg
Trimeprazine	7.5-15.0 mg
Clonidine	0.05-0.3 mg
Trihexyphenidyl	2.0-10.0 mg

I. Major Tranquilizers (Antipsychotics; Neuroleptics).

Indications

(A) *Infantile Autism of Pervasive Developmental Disorders*

Major tranquilizers reduce some of the symptoms of autism and pervasive developmental disorders of childhood(1,2). They make children more manageable, less agitated and easier to live with. They reduce the activity level, aggressiveness, temper tantrums, withdrawal and stereotype behavior and improve mood, eating, sleeping and learning(3). The interpretation of the research studies on these drugs are difficult because diagnostic criteria are different from centre to centre and the criteria of outcome are often diffuse rather than specific for target symptoms(1).

(B) *Childhood Schizophrenia*

These patients are less responsive even though hallucinations, anxiety, tension and agitation abate with neuroleptics(4).

(C) *Tourette's Syndrome*

The efficacy of major tranquilizers is

TABLE III—*Contraindications and Special Precautions Required for Various Drugs*

Drug Group	Contraindications	Special precautions
I. Major tranquilizers	Depression, subcortical brain damage (parkinsonism); impaired hepatic functions blood dyscrasias, circulatory collapse, coma	Use carefully in patients receiving other CNS depressant drugs, may lower seizure threshold, may disturb heat regulation, may produce hypotension, avoid in severe cardiovascular disorders. Butyrophenones may reduce the effectiveness of oral anticoagulants
II. Minor tranquilizers	Hypersensitivity, myasthenia gravis, acute congestive glaucoma, pulmonary insufficiency, chronic psychoses	Cardiorespiratory insufficiency, hepatic or renal dysfunction, with other CNS depressants
III. Antidepressants	Hypersensitivity, heart block, narrow angle glucoma, severe liver disease	Cardiovascular disease, epilepsy, hyperthyroiddism, glaucoma, urinary retention, renal or hepatic dysfunctions, use of other CNS depressants or anticholinergic drugs, suicidal tendencies
IV. Stimulants	Heart disease, hypertension, tics, stereotypies, schizophrenia, anxiety states, hypersensitivity	Hepatic disease, mentally retarded children, depression, chronic use, cerebrovascular or cardiac disease, glaucoma, urinary retention, anticoagulant therapy
V. Anticonvulsants		
(*a*) Carbamazepine	Bone marrow depression, hepatic insufficiency, pregnancy and lactation	
(*b*) Phenobarbitone	Acute intermittent porphyria, attention deficit disorder, Chronic pain; use with other CNS depressants, Petit mal epilepsy.	Impaired heaptic, renal cardiac or pulmonary functions, anticoagulant therapy, chronic use.
(*c*) Phenytoin valproate		Impaired, hepatic function, barbiturates enhance its metabolism while anticoagulants, INH, disulfiram and phenylbutazone increase its levels

(*d*) Succimides	Grand mal epilepsy	Blood dyscrasias, hepatic, and renal insufficiency
VI. Lithium carbonate	Addison's disease; heart failure; severe renal insufficiency, thyroid dysfunction	Dehydration or decreased salt intake, diuretic therapy, impaired renal function, pyrexia, electroconvulance therapy
VII. Central anticholinergics	Glaucoma; urinary retention, paralytic ileus, heart disease	Psychosis, pyrexia; hepatic or renal insufficiency

difficult to evaluate because of the natural waxing and waning of symptoms. Haloperidol in low doses is effective in the suppression of multiple motor and vocal tics in upto 80% of the cases(1,5). Pimozide is effective in those who do not respond to haloperidol(5,6).

(D) *Conduct Disorders*

Major tranquilizers reduce aggression, oppositional behavior and gross motor activity. These children have fewer fights and arguments with others and become more manageable and concentrate better(4). Haloperidol is, perhaps the most potent agent in improving behavior, memory and learning(7).

(E) *Hyperkinesis*

The efficacy of low doses of haloperidol in treatment of hyperkinetic disorders has been claimed to be comparable to those of methylphenidate(7).

(F) *Miscellaneous Uses*

These drugs reduce the frequency of stereotyped behaviors in severely retarded children. Because of their antiemetic and appetite stimulating effects, major tranquilizers, especially chlorpromazine have been used in anorexia nervosa(1). Major tranquilizers in small doses are superior to minor tranquilizers in the treatment of chronic anxiety, as there is no risk of dependence(2). They are, however, not indicated for insomnia, simple anxiety, non-specific behavioral problems or emotional disorders(1,2).

Adverse Reactions

The adverse reactions include anticholinergic side effects (*Table I*). Abdominal pain may occur early in treatment while enuresis has also been reported(2,8). Extrapyramidal side effects including acute dystonic reactions, parkinsonism, tremors, akathisia, rigidity and drooling are best managed either by reduction in dosages or with antiparkinsonian drugs. Blood disorders, weight gain and photosensitive rash (common with phenothiazines) may occur with prolonged use(2). Behavioral toxicity characterized by worsening of pre-existing symptoms or development of new symptoms such as hyper or hypoactivity, irritability, apathy, withdrawal, stereotypies, tics or hallucinations may occur(4). Chlorpromazine and thioridazine induce congestive dulling by sedation interfering with school

performance and hence should be avoided(5). The long term use of haloperidol may cause lethargy, feeling like 'a zombie', dysphoria, personality changes, pseudoparkinsonism, akathisia and intellectual dulling(5). Pimozide has less severe side effects but may induce ECG changes which have potential serious consequences.

II. Minor Tranquilizers

Indications

(A) *Anxiety*

There are no controlled studies of these agents in isolated anxiety disorders in children(2). Diazepam can be used as a short term treatment of children with severe anticipatory anxiety. Alprazolam is useful in avoidant and over-anxious disorders but there is a high incidence of relapse on withdrawal(9).

(B) *Sleep Disorders*

Diazepam is useful in treatment of children with severe night terrors, persistent true insomnia and somnambulism(10).

Adverse Reactions

Infants and children absorb diazepam faster and metabolize it more quickly(10). It is better to use them in small doses, for a short period and taper them off gradually to avoid the risk of rebound anxiety and withdrawal seizures(2). The common adverse effects include sedation, ataxia, confusion, emotional lability and worsening of psychosis. These drugs also produce physical dependence(11). Paradoxical or disinheriting reactions manifested by acute excitation, irritability, increased anxiety, hallucinations, increased aggressiveness and hostility, rage reaction, insomnia and inco-ordination may occur(4,9).

III. Antidepressants

Indications

(A) *Depression*

With better diagnostic criteria and reliable instruments for measuring severity of depression, imipramine has been found to be a promising agent(12).

(B) *Hyperkinesis*

Imipramine is effective in the treatment of aggressive, hyperactive and inattentive behavior(13,14). It has a positive effect on learning, motor performance and social behavior suggesting mode of action similar to methylphenidate(7). However, it is not the drug of first choice as it has many drawbacks(15). These include difficulty in maintaining the effects over time, potential cardiac side effects in prepubertal children and accidental and intentional overdose. It is thus indicated in children who do not respond to stimulants, develop significant depression on stimulants or when movement disorders are a major concern.

(C) *Enuresis*

Tricyclic antidepressants (imipramine, amitriptyline, desipramine and nortriptyline) are effective in treating primary as well as secondary enuresis(1,2). The mechanisms of action include its anticholinergic properties, anxiolytic and antidepressant effects and also, possibly alteration of sleep architecture. Frequent relapses on withdrawal of medication make

its place in treatment questionable. These agents should not be used in children under six and the duration of treatment should not exceed 8 weeks. In cases of relapse, the course can be repeated after an interval of a couple of months or in combination with behavior therapy.

(D) *School Avoidance or Separation Anxiety*

School phobias are infrequently seen in India unlike in the West. In those who are resistant to behavioral treatment, imipramine may be effective as measured by return to school and decrease in separation anxiety(15).

(E) *Sleep Disorders*

Tricyclics are used occasionally for severe night terrors or somnambulism(2,4).

(F) *Obsessive Compulsive Disorder*

Cloimipramine, which is useful in the treatment of children with obsessive compulsive disorder, is not available in India and is very costly(16).

Adverse Effects

They have anticholinergic side effects such as dry mouth, sedation, urinary retention, narrow angle glaucoma, blurred vision, nausea, anorexia, constipation, dizziness and heart burn. Most of these side effects are transient and may respond to lowering of dose. Nortriptyline and desipramine have the least anti-cholinergic effects. Cardiovascular side effects include slowing of intracardiac conduction, raising of diastolic blood pressure and heart rate(14). Behavioral toxicity characterized by irritability, worsening of psychosis, agitation, aggression, forgetfulness and confusion may occur.

Sudden withdrawal of tricyclics may lead to flu-like gastrointestinal syndrome characterized by nausea, vomiting, cramps, headache and muscle pains(2). Tricyclic drugs should be tapered off over a one to two weeks period. The shorter half life of tricyclics in prepubertal children produces daily withdrawal symptoms if medication is given once a day(2).

The efficacy and adverse effects of many newer antidepressant drugs such as trazodone, amoxapine, fluoxetine, *etc*. have not been fully evaluated in children(2).

IV. Stimulants

Two main drugs are dextroamphetamine and methylphenidate. They are the best studied psychoactive agents but at present their use is limited in children.

Indications

(A) *Attention Deficit Disorder With or Without Hyperactivity*

These drugs are useful in treating children with attention deficit disorder with hyperactivity or without hyperactivity(17, 18). All children do not respond or do so to a variable extent. The precise action of these drugs remains unclear. It is widely held that stimulants have paradoxical effects upon children and adults. In adults, the effect is stimulant while in children, it is sedating. Both dextroamphetamine and methylphenidate promote serotonin output with a net increase in monoamine activity(2).

The stimulants have a positive effect on motor activity and associated behavioral

and learning problems(17). They facilitate motor performance either by increasing speed or producing more selective control over motor responses(7). Absence of neurological signs and EEG activity and higher IQ indicate stimulant responsivity(19).

Upto two thirds of the children show improvement but the persistence of beneficial effects of stimulants after stopping treatment is doubtful. Loss of initial cognitive improvement was present when stimulants were given for a longer period in a study by Campbell(19) whereas Sleator *et al.*(20) observed that in 40% of children, behavioral improvement persisted during stimulant therapy for two years or more.

(B) *Other Uses*

Stimulants have been used for treating children with sleep disorders (somnolence and somnambulism) and enuresis but are not the drug of choice due to adverse reactions.

Adverse Effects

By the age of 3 years, the pharmacokinetics of stimulants in children are similar to that of an adult(21). The common side effects are given in *Table I*. The rare but potentially serious side effects include Tourette syndrome, growth retardation, depression, stereotyped activities, tachycardia and hypertension(22). The infrequent side effects are dizziness, nausea, nightmares, dry mouth, constipation, lethargy, fatigue, hyperacusis, rash or hives, conjunctivitis, formication and euphoria. Very occasionally, death may occur due to hyperpyrexia or intracranial hemorrhage. The side effects of pemoline include choreiform movements, night terrors, lip licking or biting and hepatotoxicity(2). Abuse potential is maximum with dextroamphetamine.

Magnesium pemoline is now the preferred drug over amphetamines. Some of its features such as once daily regimen, longer duration of action and fewer side effects particularly on growth, have put it in a practically advantageous stage(23). However, it takes about 3-8 weeks to be fully effective.

V. Anticonvulsants

Indications

(A) *Conduct Disorders*

Children with severe impulsive aggression with emotional lability and irritability, who have an abnormal EEG or a strong clinical suggestion of episodic phenomenon may deserve a trial with carbamazepine(24).

(B) *Epilepsy with Behavior Disorders*

Phenobarbitone increases activity and behavior disorders in about 15-20% of children on therapy. The rate is higher in children with brain damage, psychomotor epilepsy or those who are on multiple anticonvulsants(1). These effects can appear at therapeutic blood levels and a lowering of dose does not abate these effects. Phenobarbitone, because of its dependence potential, narrow safety margin and fatality in overdoses is not a preferred drug in children. Phenytoin may impair cognitive functions and scholastic performance(2). Carbamazepine is the preferred drug in these children.

(C) *Maniac Depressive Psychosis*

Carbamazepine is useful in the

prophylaxis and treatment of children with maniac depressive psychosis(25). It is effective in patients who do not respond to lithium and it has fewer side effects.

Adverse Effects

The adverse effects of carbamazepine are given in *Table I*. The adverse behavioral reactions include extreme irritability, agitation, insomnia, obsessive thinking, aggression, hallucinations, delirium, paranoia, hyperactivity, and psychosis may be seen in 1 to 4 weeks of treatment(24,26). Phenobarbitone is associated with impairment of memory and attention, hyperactivity, irritability, aggression and dysphoric mood(24).

VI. Lithium Carbonate

(A) *Maniac Depressive Psychosis*

The indication of lithium is bipolar effective disorder, mixed or mania but it is not indicated for prophylaxis in children unless there is a very well documented history of recurrent episode(1,2).

(B) *Aggression*

Lithium is indicated in controlling aggression which is impulsive and accompanied by explosive effect(2). It is superior to haloperidol in reducing aggression, hostlity and tantrums with fewer side effects. Lithium is also useful in mentally retarded children with severe aggression directed towards themselves or others. Lithium therapy improves learning and motor co-ordination(4).

Adverse Effects

The common side effects are given in *Table I*. Children may experience side effects at lower serum levels than adults. Toxicity is related to serum levels and there is a narrow therapeutic margin. The symptoms of lithium toxicity include vomiting, drowsiness, hyperreflexia, sluggishness, slurred speech, ataxia, anorexia, convulsions, stupor, coma and death.

VII. Miscellaneous Drugs

(A) *Antiparkinsonian Agents (Central Anticholinergic Agents)*

These are used to treat extrapyramidal side effects of neuroleptics in adolescents and rarely in children. They aggravate psychosis and the anticholinergic side effects of neuroleptics. These drugs cause euphoria and may mask the tardive dyskinesia caused by neuroleptics.

(B) *Antihistaminics*

Diphenhydramine, promethazine, trimerprazine and hydroxyzine are useful in sleep disorders, anxiety and hyperactivity. Promethazine and diphenhydramine are also used for treating acute dystonic reactions. The common adverse effects include dizziness, over-sedation, in co-ordination, blurred vision, dry mouth, nausea, abdominal pain, agitation and acute dystonic reactions. With chronic administration, these drugs may cause tardive dyskinesia. Because of their anticholinergic side effects, they may precipitate glaucoma and urinary retention(2).

(C) *Chloral Derivatives*

They are often used as hypnotics in children. They have a wide safety margin but are less effective than the benzo-

diazepines when given on a chronic basis. They may cause mild gastric irritation.

(D) *Fenfluramine*

It is structurally similar to amphetamine and is an appetite suppressant. In autistic children, it increases social relatedness, improves communication and decreases irritability, temper tantrums, aggressiveness, self mutilation and hyperactivity. Approximately one third of autistic children are strong responders, at least in short term(4). The adverse effects include weight loss, stomach upset, constipation, diarrhea, drowsiness, lethargy, withdrawal, crying, sleep disturbances, agitation and excessive irritability. The long term safety of fenfiuramine has not yet been demonstrated.

(E) *Clonidine*

It is an alpha-adrenergic agonist used for treatment of hypertension. Nearly 40-70% of patients with Tourette syndrome benefit although a recent report is more pessimistic(27). Clonidine may be helpful in improving attentional problems and in alleviating complex motor and vocal tics(5). The combination of small doses of haloperidol and clonidine is successful for patients who cannot satisfactorily be treated by either medication. Clonidine may prove useful in improving the behavior of children with attention deficit disorder(5).

It is useful at a low dose and should be titrated gradually over weeks and tapered rather than stopped immediately to avoid a withdrawal syndrome consisting of exacerbation of tics, motor restlessness, blood pressure and pulse rate(28). The most troublesome side effect is sedation, although it tends to decrease after several weeks. Dry mouth, photophobia and dysphoria have also been reported, though hypotension and dizziness are possible in high doses(5).

(F) *Propranolol*

The beta-adrenergic blocker may be useful in patients with otherwise uncontrollable rage reaction and impulsive aggression especially those with evidence of organicity(29).

(H) *Nifedipine*

Nifedipine, a calcium channel blocker, is useful in improving behavior and also reducing the vocal as well as motor tics(30). Its mechanism of action is believed to be a reduction in calcium influx to the presynaptic neurone resulting in decreased transmitter release. However, the use of this drug needs further replication by controlled trials as spontaneous remission of tic disorder is not uncommon.

The above review of role of drugs in childhood psychiatric disorders reflects that drugs help to aid other methods of treatment, *e.g.,* psychotherapy, behavior therapy, *etc.* In most instances, these drugs suppress the symptoms and help in many ways. Firstly, the amelioration of symptoms makes the child amenable to psychotherapy. Secondly, it will permit the child to develop normally and lastly, it will give a sign of relief to parents and those around the child.

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