Global Journal of
Pharmacy & Pharmaceutical Sciences
ISSN: 2573-2250

Juniper Publishers
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Review Article
Volume 5 Issue 5 - July 2018
DOI: 10.19080/GJPPS.2018.05.555675

Glob J Pharmaceu Sci

Disorder of Infancy and Childhood: A Review

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Submission: July 05, 2018; **Published:** July 20, 2018

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Abstract

During the last decade, a substantial scientific base has been established for psychopharmacology of adult patients. Diagnostic precision for treatment has been facilitated by the continuing revision of the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders. The increasing confidence with the data thus generated regarding psychotropic drugs has also increased attention to child and adolescent psychotropic drugs in child and adolescent population have been conducted despite their frequent use. This review will focus on three diagnostic whose primary treatment is medication-attention deflect hyperactivity disorder, functional enuresis, and Tourette's disorder. Using psychotropic drugs to treat children and adolescents often requires a very different approach than when the same drugs are used for psychiatric disorders among adults. Most adults given psychotropic drugs suffer from major and major depression. Despite well-defined diagnostic criteria, many children are given psychotropic drugs merely to control a group of symptoms or behavior in order to facilitate the child's learning and development. The psychiatric assessment of a child requires obtaining information from the child, the parents or caretakers, and teachers.

The overall diagnostic impression is formed from psychiatric, social, neuropsychologic, and educational evaluations. Before the initiation of psychotropic drugs, the child and family need to be familiar with the risks and benefits of drug therapy, any alternate therapies, and possible adverse effects including drug withdrawal. In addition, and idiosyncratic effects should be presented. The risks of untreated illness should also be discussed. Pharmacotherapy for children and adolescents is usually administered in conjunction with other therapies (e.g., psychotherapy, family therapy, or behavioral therapy). Medication should not be used in place of other therapies or because other therapies have failed. Careful documentation of baseline symptoms is necessary before initiating drug therapy to identify the responsive symptoms and established a realistic expectation for treatment outcome.

Keywords: Psychotherapy; Neuropsychotherapy; Psychiatric disorder; Behavioral therapy; Psychotropic drug

Introduction

Attention-deficit hyperacidity disorder (ADHD)

The three essential features of ADHD are signs of developmentally inappropriate inattention, impulsivity, and hyperactivity. Inattention typically involves the child failing to finish tasks, not seeming to listen, being easily distracted, having difficulty concentrating on schoolwork, and having difficulty sticking to a play activity. Impulsivity is manifest as often acting before thinking, shifting excessively from one activity to another, difficulty in organizing work, needing much supervision. Frequently calling out in class and difficulty awaiting a turn in games or group situation. Hyperactivity typically includes excessive running about or climbing on things, difficulty sitting still or staying seated, excessive movement during sleep, and acting as "driven by a motor." Symptom presence and severity are variable with the situation of the disorder in all setting or even in the same setting at all times [1]. The onset of ADHD is typically by the age of 3 and must be by age 7, though the disorder may not require professional attention until the child enters school. Approximately 10% of boys and 2% of girls have ADHD, with the general prevelance in school age children estimated at 6%.

Pathophysiology

ADHD involves multiple etiologies. Family studies indicate a genetic component [2]. Early investigators suggested that children with ADHD are chronically underaroused and stimulants induce a state of normalization. Other investigatiors have suggested the opposite that the children with ADHD are overaroused and that the stimulant drugs calm the patients. More recently it has been proposed that ADHD is not a high or low state but a dysequilibratory disorder of the frontal-neostriatial dopamine systems with widely varying states of arousal. Children with ADHD tend to have phasic outbursts of activity and inactivity resulting in insufficient alertness during dull and repetitive tasks and overarousal at other times resulting in ineffective performance. Stimulant drugs may serve as a homeostat to

stabilize responses and thereby prevent the spontaneous fluctuations that are characteristic of ADHD [3].

Pharmacological strategies for the treatment of ADHD

Stimulants: Dextroampheamine, methylphenidate, and pemoline represent the most effective drug treatment options. The stimulants decrease motor activity and impulsivity and increase attention span. Efficacy is optimal when the diagnosis is clear- cut, classic target symptoms are rather than preschool [4]. In addition to behavioral effects, stimulants may improve cognitive performance. For example, reading, memory, and arithmetic performance is often significantly improved. Improved cognitive performance possibly results from an overall increase in attention and concentration, not to a specific effect on cognition [5]. Amphetamine were the first drugs to be used for ADHD. In a majority of patients, dextroamphetamine improves symptoms in a majority of patients and is significantly more effective than placebo. Methylphenidate is also an effective drug for ADHD. Efficacy studies repory a 70% to 90% response rate as well as clear superiority over placebo [6]. Pemoline, the most recently introduced effective drug, is more effective than placebo and either slightly less effective than or equal in efficacy to dextroamphetamine and methylphenidate. Two other stimulant drugs have been tried but found inferior in efficacy to dextroamphetamine, methylphenidate, and pemoline. Deanol looked promising in open clinical trials, but subsequent controlled studies found its efficacy only slightly greater than placebo. Caffeine also showed early promise, but most of controlled studies failed to establish efficacy [7,8].

Tricyclic Antidepressants (TCAs): Imipramine and desipramine, are the most systematically studied TCAs in the treatment of ADHD. Overall, imipramine and desipramine are more effective than placebo for hyperactivity with minimal to no drug effect on the other symptoms of ADHD [9-12]. TCAs are inferior in efficacy compared with stimulants for the treatment of ADHD. Patients unresponsive to stimulants have shown the greatest therapeutic response to imipramine and desipramine, suggesting these patients may represent a subpopulation of ADHD. Children with ADHD and concurrent symptoms of conduct disorder, depression or anxiety may respond better to a TCA compared with stimulants, although several studies have shown these additional symptoms tend to respond poorly [13]. Antidepressants are secondary alternatives to the stimulants for treatment of ADHD. Potential benefits of TCAs in comparison with stimulants include a longer duration of action, less sleep disturbance, reduced risk of abuse, and a lack of growth suppression, whereas their negative aspects include decreased efficacy, tolerance, many adverse effects, and the risk of death in overdose.

Monoamine Oxidase Inhibitors (MAOIs): Because stimulants inhibit the enzyme monoamine oxidase, MAOIs have been evaluated for their potential efficacy in ADHD. Tranylcypromine and clorgyline, an investigational drug specific for MAO type-A isoenzyme, have been compared with dextroamphetamine in the treatment of ADHD [14]. The MAOIs onset of activity and clinical efficacy was indistinguishable from dextroamphetamine. Tranylcypromine and clorgyline were administered in 5mg doses in the morning and at noon. Dextroamphetamine 10mg was administered in the morning and 5mg at noon. Caretakers and children were instructed on the low-tyramine diet and the need to avoid the use of sympathomimetic drugs. The adverse effects of MAOIs were mild sleepiness and decreased appetite. No significant changes in orthostatic blood pressure or pulse were observed. Further investigations are necessary to verify these reports of efficacy and safety in the treatment of ADHD. The ability of children to follow a low tyramine content in diet in unsupervised situations is a major consideration in the use of MAOIs.

Other treatment options

Bupropion, a monocyclic antidepressant, is unique as a mild dopamine uptake inhibitor with no direct effect on serotonin, norepinephrine, or monoamine oxidase. Bupropion was compared to placebo in a 6-week controlled trial in 30 children with ADHD [15]. Bupropion was initiated at 3mg/kg and titrated to 6mg/kg over 15 days of therapy. The response bupropion was better than placebo on the overall assessment as well as a subsection of the teacher's questionnaire on hyperactivity. Bupropion was not more efficacious than placebo on the parent's questionnaire or the teacher's questionnaire on conduct. Future investigations are required to determine the role of bupropion in the treatment of ADHD.

Clonidine, a central α2 adrenergic agonist, inhibits noradrenergic activity by decreasing the release of norepinephrine from the presynaptic neuron. Controlled studies suggest that clonidine is more effective than placebo in reducing the hyperactivity and impulsive in children with ADHD [16]. Clonidine was initiated at 0.05mg/d and increased by 0.05mg every other day until a divided daily dose of 0.004 to 0.005mg/kg was administered. Fenfluramine, an amphetamine derivative, has dose dependent effects on serotonin activity-low dose result in increased serotonin activity, whereas high doses result in decreased serotonin activity. Fenfluramine also has central dopamine releasing and norepinephrine reducing properties. Despite fenfluramine's chemical similarity to amphetamines, a controlled crossover trial of fenfluramine and dextroamphetamine reported no therapeutic activity of fenfluramine in ADHD [17].

Conclusion: At this time, the best approach to treating ADHD is either dextroamphetamine or methylphenidate for patients with moderate to severe symptomatology. Pemoline remains a secondary treatment option for those who cannot tolerate multiple daily dosing of first line drugs because of insomnia or loss of evening appetite.

How to cite this article: Amrish Kumar, Vrish D A, Mansi V. Disorder of Infancy and Childhood: A Review. Glob J Pharmaceu Sci. 2018; 5(5): 555675. DOI: 10.19080/GJPPS.2018.05.555675.

Functional Enuresis

The essential feature of functional enuresis is repeated involuntary or intentional voiding of urine by day or at night not caused by any physical disorder. Noctural enuresis typically occurs 0.5 to 3 hours after sleep onset. Children with daytime enuresis usually have nocturnal enuresis. Rare physical causes of enuresis (e.g., diabetes, seizure disorders or urinary tract infections) should to be ruled out. Diagnostic criteria for functional enuresis have been defined as involuntary voiding of urine at least twice a month for children between 5 and 6 years of age, and once per month for older children. There are two diagnostic categories of enuresis, primary and secondary. Primary functional enuresis occurs in 80% of children with functional enuresis and refers to children who have not experienced a 1-year period of continence. In the secondary type, enuresis follows a 1-year period of urinary continence. At age 5, prevelance is 7% for boys and 3% for girls, and at age 10, it is 3% for boys and 2% for girls. Most children will "out-grow" functional enuresis, as at age 18 only 1% of boys and virtually no girls still have the condition [18].

Factors that predispose a child to either type of enuresis include delayed or lax toilet training, small bladder capacity, and psychosocial stress. The psychiatric disorders most commonly associated with enuresis are depression and developmental delays. In addition, children with nocturnal enuresis do not have the normal diurnal nighttime increase in antidiuretic hormone (ADH) [19]. Urination is not associated with a particular sleep stage, it typically occurs in the deeper stages of non-rapid eye movement(non-REM) sleep, but also can occur during the REM stage of sleep [20].

Pharmacological Strategies for the Treatment of Functional Enuresis

Trycyclic antidepressants

Drug therapy is reserved for those children who have not responded to an adequate trial of dry bed training or the bed-wetting alarm methods of therapy. Exceptions to the secondary role of drug therapy are when the child is at risk of physical or psychological harm from the caretaker. TCAs are rapidly effective in the treatment of enuresis, whereas dextroamphetamine, MAOIs, and anticholinergic drugs are ineffective.

The exact mechanism of action of TCAs in treating enuresis is unknown, however previous theories (elimination of stage 4 sleep and peripheral anticholinergic effects) have been ruled out as explanations. Imipramine is the most studied TCA, although others are also effective. The initial dose of imipramine should be 25mg at bed time, with weekly increase of 25mg, if necessary. A nightly dose greater than 75mg is rarely necessary. Effect is often immediate and is usually evident within 7 days. Drug plasma concentrations of dopamine and desipramine do correlate with clinical response, and true nonresponders exist in spite of adequate plasma concentration [21]. Imipramine efficacy is about 85%, one half of patients experience total elimination of bed wetting, and the other half, a significant decrease in the number of episodes. An initially effective dose often becomes ineffective in 2 to 6 weeks but increasing the dose usually reestablishes control. One week is needed to evaluate the efficacy of a new dose.

Desmopressin

Desmopressin, a synthetic analogue of the natural human antidiuretic hormone arginine vasopressin, is available in a nasal spray for the treatment of nocturnal enuresis. The mechanism of action is an antidiuretic effect that raises overnight urinary osmotic concentration by increasing water reabsorption and reducing the volume of urine entering the bladder. The initial recommended dose is 20µg at bedtime, increasing to 40µg per night after 3 days if there is no response. Some patients may respond to as little as 10µg. Half of each dose in administered per nostril. About 10% of the dose of desmopressin is absorbed from the nasal mucosa, plasma concentration reaches a maximum about 45 minutes after administration. Biologic half-life is 4 to 6 hours and the duration of action varies from 6 to 24 hours [22]. Children treated with desmopressin compared with enuresis alarms are significantly dryer during the first

Few weeks of therapy, after 3 months, the therapies are equally efficacious, but immediate relapse after discontinuation of therapy is markedly higher in the drug group than the enuresis alarm group. The best response rate to desmopessin appears to occur in children over the age of 9. Patients with colds or allergies that affect the nasal mucosa may have a less than optimal response to desmopressin. Rare adverse effects include irritation of the nasal mucosa, epitaxis, rhinitis, nasal congestion, transient headache, chills, dizziness, nausea, and abdominal pain. Water intoxication, hyponatremia, and tonic-clonic seizures have also been reported [23].

Conclusion

Both TCAs and desmopressin are effective in the treatment of nocturnal enuresis. Drug therapy selection for the individual patient is based on the drug adverse effect profiles, ease of administration, and cost. Overall, imipramine has a higher incidence of adverse effects than does desmopressin and the risk of accidental overdose with a TCA is of concern. In contrast, desmopressin nasal spray requires a specific administration technique and is more expensive than imipramine. If drug treatment needs to be given longer than several weeks, then attempts to discontinue the drug every 3 to 6 months are advisable, as spontaneous remission occurs at a rate of 15% per year. Before drug treatment begins, an accurate baseline record of bed-wetting frequency must be recorded.

Tourette's Disorder

This rare disorder of the central nervous system is a lifelong syndrome of recurrent, involuntary, repetitive, rapid, and purposeless motor movements of multiple muscle groups,

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generally accompanied by involuntary vocalization (throat clearings, coughing, hissing, barking like noises. Snorting, echolalia, and obscenities), any or all may be voluntary suppressed from minutes to hours.

Pathophysiology

An understanding of the various proposed etiologies of this disorder is necessary to allow for an understanding of the variety of treatment approaches used. The successful use of haloperidol by Seignot in France in 1961 was rapidly followed by other successful reports. This led reaserchers to believe that the syndrome was a disorder of dopaminergic activity in the corpus striatum. The frequent exacerbation of illness in a patient previously well controlled on haloperidol leads researchers to attempt other drug therapies. Success with other treatment methods has modified the simplistic dopamine hypothesis. The currently accepted theory is that Tourette's is a genetically based disorder of central neurotransmitter activity, 47% of female and 28% of males have a positive family history [24]. This disorder involves an imbalance in the interaction of dopaminergic, serotonergic and noradrenergic system. This multiple system etiology best explains the success of a variety of effective treatment options.

Heloperidol

Haloperidol remains the treatment of choice for Tourette'a disorder, as it is usually effective at low dose dosage and is well tolerated. Despite its long history of use, there is only one adequately controlled study supporting the efficacy and superiority of haloperidol over placebo [25]. Haloperidol is effective in decreasing the frequency of tics but has limited effect on comorbid disorders such as ADHD. Therapy with haloperidol should be initiated at very low doses of 0.025-0.05mg/kg/d and increased gradually to avoid extrapyramidal side effects and excessive drowsiness. The daily amount should be divided into two or three doses and increased by small increments over a 2 to 3week period until symptoms are controlled. The dosage should be read justed to the lowest level that will provide symptoms control with the least amount of troubling side effects. Symptoms may regress within 24 to 48 hours after therapy is initiated and may disappear with proper dosage adjustments [26]. Many patients are maintained on daily doses smaller than 10mg of haloperidol for long periods of time, but the dosage required may very between 6 and 180mg/d. Such treatment generally results in improvement in about 90% of patients.

Pimozide

Approved for marketing in the United States in 1984 as an orphan drug, pimozide represents an alternative to haloperidol for Tourette's disorder [27]. Pimozide a diphenylbutylpiperidine differs structurally from phenothiazines and butyrophenones. Pimozide possesses selective central dopamine-2 receptor blockade and calcium chammel antagonist activity with no effect on noradrenergic receptors. It's elimination half-life in children with Tourette's disorder is approximately 66 hours, with Tourette's disorder is approximately 66 hours, with a variable range or 24 to 142 hours. The metabolites of pimozide are inactive. Most efficacy studies show pimozide to be equal or slightly less effective than haloperidol. The efficacy of pimozide may be limited by the maximum dosage requirements from the food and drug administration.

Clonidine

Clonidine is used with some success in patients who do not respond to or cannot tolerate haloperidol or pimozide. Additional effects of clonidine on serotonergic, dopaminergic, and opioid system are mediated through its central adrenergic agonist effects. The efficacy of clonidine in Tourette's disorder is controversial. For some patients, the response is limited to attentional and behavioral problems with no change in the frequency of tics [28]. Clonidine is generally well tolerated as long as treatment is initiated with a single test dose (generally around 0.05mg) given in the morning and blood pressure is carefully monitored. If the test dose is tolerated, treatment is begun with a 0.05mg daily dose, titrated upward every 4 to 7 days to the maintenance dose of 0.15mg administered in divided daily dose. This dose may need to be further increased slowly over several weeks to control symptoms. This treatment approach is effective, with a gradual onset of action over 2 weeks to several months, in a subpopulation of patients [29,30].

Conclusion

At this time the best approach for the treatment of tourette's disorder is Haloperidol at the lowest dose possible, with clonidine or pimozide as secondary agents in those patients not responding or intolerant to haloperidol.

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DOI: 10.19080/GJPPS.2018.05.555675

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