Advances & Considerations in Pharmacotherapy of Attention-deficit / hyperactivity disorder (ADHD)

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral condition primarily affecting children but regularly persisting into adolescence and adulthood. The symptoms must present in multiple settings ie home, school, work, be inappropriate for developmental level and interfere with the individual's level of functioning, social development, learning processes, and quality of life. There are three presentations of ADHD i.e. inattentive, hyperactive and combined. There is a substantial pharmacopoeia available for safe and effective treatment of ADHD. CNS stimulants like methylphenidate, amphetamine are recommended as first-line medication therapy for children. It includes various class of drugs like centrally acting sympathomimetic, anti-psychotic, anti-depressant (SSRI), alph2 agonist and some newer agent like atomoxetine in the treatment of ADHD. ADHD remains the only highly prevalent, nondegenerative neuropsychiatric disorder for which effective medications remediate the principal cognitive disturbances in concert with clinical efficacy. Therefore, deeper insight into the neural mechanisms of cognitive remediation may serve to advance treatment development not only in ADHD, but across a wide range of neuropsychiatric disorders in which cognitive dysfunction is a cardinal feature and a strong predictor of clinical outcome. All effective medications for ADHD act on one or both of the major catecholamine neurotransmitter systems in the brain. These 2 systems, which arise from subcortical nuclei and use of norepinephrine (NE) or dopamine (DA) as transmitters exert strong modulatory effects on widely distributed cortical–subcortical neural circuits, with important effects on cognition, mood and behavior in both health and illness.

Keywords: Atomoxetine, Methylphenidate, Pathophysiology, Psychostimulants.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in childhood and adolescence and has an estimated worldwide prevalence of approximately 3.4% to 7.2% [1-2]. ADHD is a consistent pattern of behaviors causing the inability to maintain sustained attention and focus and increased impulsivity that affects an individual in multiple settings [3]. There has been a 42% increase in the diagnosis of childhood ADHD from the years 2004 to 2012 [4].This places a financial and social burden on society as the cost of health care continues to rise and mental health care becomes more limited [5].The Diagnostic and Statistical Manual of Mental Disorders (DSM), sets guidelines for the diagnosis of mental health disorders. The 5th edition, released in May 2013, was its first major revision since 1994 [6]. Primary care providers (PCPs) are on the front-line for the screening and diagnosis of ADHD, diagnosing nearly 53.1% of cases [7]. It is one of the most common psychiatric conditions estimated to affect 5-10% of all children and predisposes them to impaired academic, familial, social, vocational, and emotional functioning if untreated [8-9]. ADHD is characterized along two symptom domains, inattention-disorganization and hyperactivity impulsivity. Individuals with ADHD have significant difficulty in the areas of attention, response inhibition, and self-regulation. The effects of ADHD are life encompassing and are not limited to the 8-hour school day. Usually, some symptoms that cause impairment are present before age seven. Classification of what constitutes ADHD has changed

dramatically over the last two decade, with successive revisions of the Diagnostic and Statistical Manual four (DSM) [10]. Current DSM IV classification for combined type ADHD requires a minimum of six out of nine symptoms of inattention and a minimum of six out of nine symptoms of hyperactivity/impulsivity. In addition some impairment from the symptoms is present in two or more settings (e.g., at home and at school) and clear evidence of significant impairment in social, school, or work functioning. The DSM IV also allows the classification of two subtype disorders: (i) predominantly inattentive where the child only meets criteria for inattention; and (ii) predominantly hyperactive–impulsive where only the hyperactive–impulsive criteria are met [11-12]. Effective treatment depends on appropriate diagnosis of ADHD. A comprehensive medical evaluation of the child must be conducted to establish a correct diagnosis of ADHD and to rule out other potential causes of the symptoms. ADHD can be reliably diagnosed when appropriate guidelines are used [13-17].

EPIDEMIOLOGY

The worldwide prevalence of ADHD continues to increase [18]. The US prevalence of children diagnosed with ADHD was 7.8%, 9.5%, and 11% in 2003, 2007, and 2011 respectively, representing nearly 6.4 million children. Compared with 2003, in 2011 there were nearly 2 million more children diagnosed with ADHD and 1 million more children prescribed medication for ADHD. The number of visits to ambulatory care centers for evaluation and management of ADHD is increasing, according to analyses of insurance claims filed between 2001 and 2010, although this may not represent the uninsured [19]. Teachers identify fewer girls than boys with ADHD symptoms. The prevalence of ADHD is higher in boys with an estimated male/female ratio between 4:1 and 9:1 [20]. The median age for diagnosis is 7 years old, with one-third of total children being diagnosed before age 6 years [21]. The inattentive type is the most common presentation [22]. The prevalence is increasing for several reasons. Increased awareness and social acceptance of the disorder give parents and teachers confidence to request behavioral evaluations for their children or students. Improved screening tools and PCP knowledge increase diagnosis rates. More sophisticated health care has improved the survival of infants who are at increased risk for neurobehavioral disorders. This increased prevalence greatens the societal need for mental health, education, and social services and demands PCPs assume the responsibility of assessment and management of this chronic disorder [23].

ETIOLOGY

The causes of ADHD are unknown. Most children with ADHD have no evidence of gross structural damage in the central nervous system. ADHD does appear to run in families with approximately one-third of affected children having a first degree relative with a history of ADHD [24]. Recent functional MRI brain studies indicate that the disorder may be caused by atypical functioning in the frontal lobes, basal ganglia, corpus callosum, and cerebellar vermis. Pharmacological studies have also implicated dysregulation of frontal-subcortical-cerebellar catecholaminergic circuits in the pathophysiology of the disorder. Central catecholaminergic neurotransmission systems appear to be involved in the pathophysiology of ADHD. Effective medication treatments for ADHD appear to modulate dopaminergic and noradrenergic neurotransmission in the prefrontal cortex. Children with ADHD as a group show differences from unaffected children in the volumes of specific brain regions in imaging studies (i.e., frontal lobes, temporal gray matter, caudate nucleus, and cerebellum) [25]. The cause of such differences is unknown and brain imaging is not useful as a diagnostic tool if used to differentiate youth with ADHD from those without. Traumatic brain injury has been associated with ADHD but probably accounts for ADHD in only a small percentage of affected children [26]. Environmental factors may also be relevant. Exposure to maternal tobacco or alcohol use in utero may increase the risk of ADHD in offspring. Exposure to lead early in life has also been associated with ADHD. Though up to 5% of children with ADHD may respond to dietary manipulations for food allergies, there is little evidence that exposure to refined sugar or food additives are responsible for ADHD in most affected children [27-29].

PATHOPHYSIOLOGY

The idea that dysregulation of dopamine and norepinephrine circuits triggers ADHD was primarily proposed by the action of drugs for the disorder, which upsurge the synaptic availability of these neurotransmitters and by animals showing that abrasions in dopamine pathways create animal models of ADHD [30]. As one of the most enthralling animal models of ADHD, the spontaneously hypertensive rat [31] shows dopamine release anomalies in subcortical structures [32]. Because executive dysfunction is common. Executive functions, which are controlled by frontal subcortical circuits, include inhibition, working memory, set-shifting, interference control, planning, and sustained attention [33–34]. This pattern of dysfunction has led to much debate about what core neuropsychological deficit might cause both ADHD symptoms and neuropsychological deficiencies. Candidates for core arrears include failure of inhibitory control [35], dysregulation of brain systems facilitating reward and response cost[36-37] and arrears in arousal, activation, and effortful control [38-39]. Arrears in arousal and effort lead to state-dependent cognitive arrears and a view of ADHD that emphasize in regulating cognitive functions rather than core arrears in any single function. But, because no single neuropsychological theory can explain all ADHD features, neuropsychological deficiencies of the disorder could be heterogeneous and this heterogeneity probably resembles to causal heterogeneity [40]. One study has reported extensive, albeit small volume reductions throughout the brain, another has shown extensive cortical abnormalities [41] and others have involved structures such as cerebellum and corpus callosum, which are outside the frontal-sub cortical circuits [42]. Functional neuroimaging studies have considered the degree of brain activation linked with neuropsychological tasks of attention and disinhibition. Because tasks are assembled so that ADHD and control individuals do similarly well, activation differences specify group differences in the neural systems used to achieve the tasks. These studies are unfailing with the structural studies locating abnormalities of brain activation in patients with ADHD in fronto-subcorticalcerebellar circuits [43]. In the subcortical structures allied with ADHD, the striatum has been of specific interest because it is ironic in dopaminergic synapses [44], is weak to the perinatal hypoxic complications associated in the disorder, and if not intact, it produces hyperactivity and deprived inhibitory control [45].

DIAGNOSIS AND ASSESSMENT

Diagnosis and assessment for ADHD varies from clinicians, teachers, and parents. Usually assessment involves a medical examination, a clinical interview, parent and teacher ratings of behavior regarding attention, direct observation, or a combination of all of the above. Clinicians are usually interested to see if a child meets certain diagnostic criteria (DSM criteria) and teachers are typically more interested in developing a behavior management plan for use in the classroom. On the other hand, parents are usually concerned with why their child behaves inappropriately and how they should respond to this behavior [46-47].

TREATMENTS

Many treatments are currently available for ADHD. These treatments consist of three general approaches; pharmacological therapy, behavioural treatment and a combined approach. Over the past decade, numerous scientific studies have examined each treatment to establish which are most effective. Pharmacological treatment has a greater effect on behaviour than counselling, however counselling results in better educational outcomes [48]. Results from a large scale study showed that both the pharmacological and combined approaches show a significantly greater improvement in ADHD symptoms than behavioural treatment alone [49]. There is still an ongoing debate as to which drug is the most effective for general ADHD treatment. Since each approach has its strengths and weaknesses, it is prudent for healthcare specialists to decide treatments on a case-by-case basis. The American Academy of Pediatrics (AAP) issued modern clinical practice guidelines for the treatment of school-aged children (six to 12 years) with ADHD in 2001. Clinical guidelines are also being developed by the National Institute of Clinical Excellence (NICE) in the UK for treatment of ADHD [50].

CENTRALLY ACTING SYMPATHOMIMETICS

The primemedication used for the management of ADD are centrally acting sympathomimetics, like methylphenidate, dextroamphetamine and

magnesium pemoline [51]. Dextroamphetamine was formerly used in 1937 and continuous to be the drug of choice till late 1960s, when use of methylphenidate was increased with the results of less side effects with the latter drugs. It was witnessed that these reports of greater protection with methylphenidate are of great clinical importance [52]. There are studies which shows greater clinical effectiveness of methylphenidate [53] over dextroamphetamine by the authorities who use to prefer former drug, whereas exponents of dextroamphetamine shows that it has equivalent clinical efficacy at a low cost [54]. Most of the studies show that the centrally acting sympathomimetics indicate their efficiency in about 70-80% of the affected children. The medication is useful in increasing attentiveness and decreasing hyperactivity, but it may also be useful in alleviating the deficit in fine motor coordination, especially handwriting [55]. Estimation of main symptoms is important as some of the researchers have examined that low doses of stimulants helps in improving cognitive performance while higher doses are doses are used for the control of undesirable behavior [56].

Methylphenidate

Methylphenidate is a prototype drug for pharmacotherapy of ADD. On the other hand, drugs used in other disorders, the dosing of methylphenidate and other agents are pragmatic due to lack of sensitive analytical methods prior to 1980s. Current studies show that oral methylphenidate has a lag phase of 0.5-1.0 hour and attains a peak 2.5 hours after administration with a positive correspondence between plasma levels and response in ADD [57]. The drug is given orally in doses of 0.3-1.5 mg/kg BID; therapy should be started with a dose of 0.3 mg/kg in morning or twice a day so as to avoid the potential iatrogenic insomnia which can occur due to the drug. If the response is not satisfactory after 2 week the dose can be increased by 0.1 mg/kg every 2 weeks until the maximum dose is reached, and again if the dose is insufficient another medication is recommended. Dose of 10-20 mg BID shows a good response but the daily dose should not exceed than 80-120 mg [58]. Methylphenidate reduces the hyperactivity and restlessness, prevent distraction and increase the attention span with response rate of 72-85%. Secondary action of the drug is to increase learning ability. Motor ability and coordination are also improved [59]. Methylphenidate may also grounds some side effects such as suppression in growth with both weight and height reduction has been noted [60], but with the removal of drug over a period of time, an impulsive increase in growth returned the treated children to controlled levels [61-62]. In a study, it was found that there was no decrement in growth of children being treated with methylphenidate, dextroamphetamine or imipramine/desipramine for long time [63]. Nowadays, the treatment methodology allow the child to remain drug free over a longer period of time i.e. over weekend and vacations so as to elude any retardation in growth and to allow for continual reevaluation of the need of pharmacotherapy [64]. If the child's hyperactive behavior continues at home and school, drug free regime would be a problematic compliance issues. Cardiovascular side effects such as increased diastolic blood pressure or tachycardia have been noted. Insomnia and anorexia resulting in weight loss also occur but are less communal with other amphetamine derivatives. Some cases of Gilles de la Tourette's syndrome have been reported [65]. Methylphenidate inhibit hepatic drug metabolism and half-lives of several substances such as ethyl biscaumacetate, desipramine and phenytoin which results in potential toxicity. It is important to examine the possible interactions with the anticonvulsant drugs, as these are usually used concurrently in children with ADD, and causes ataxia in children treated with phenytoin and methylphenidate [66].

Dextroamphetamine

Dextroamphetamine is also used in the management of ADD, just like methylphenidate, although certain studies show similar clinical efficacy about 10-15% higher symptoms improvement has been found with methylphenidate. Usually dose if 5-20 mg BID of dextroamphetamine is used or sustained-release forms are also available for single morning dose. Tablets of 5 mg provide wider range for dose adjustment and better determination of clinical response over a period of time [67]. Dextroamphetamine shows maximum response after 1-2 hr of dosing and its duration of action is 4-6 hrs. The therapy is initiated with a dose of 5mg BID upto

an effective level by increasing the dose by 5mg/dose every 2-3 day till either the symptoms lessen or side effects are likely to occur. It has a short half life of 4-6 hours and is taken in two or three daily doses. Side effects are similar to those of methylphenidate although it may cause a more severe headache [68]. Persistent insomnia can be treated with a mild hypnotic agent like diphenhydramine (25 mg) or occasionally be ameliorated by discontinuing the dextroamphetamine and starting the therapy with methylphenidate. When this type of change is made, then a gap of 24 hrs should be taken before the initiation of new therapy. The abuse of psycho stimulant agents by children was a cause of concern, but nowadays, studies shows that abuse of drug is not a part of amphetamine therapy [69-70].

Amphetamine Salts

Adderall is commonly used to treat ADHD. It is a mixture of amphetamine salts consisting of three forms of d-amphetamine and one of 1-amphetamine. Studies have shown that Adderall is at least as effective as methylphenidate at reducing ADHD symptoms and improving academic performance38. Its dose range is between 2.5mg/day and a maximum of 40mg/day. Its effects are longer lasting than methylphenidate due to its longer half life of 6 or 7 hours [71]. Alike to methylphenidate, Adderall produces side effects comprising restlessness, dizziness, headache, insomnia, dryness of the mouth and weight loss. Sudden death has occurred in some patients taking this medication, which has resulted in the suspension of sales in some countries [72]

Magnesium pemoline

Magnesium pemoline is also used in treating ADD. This is a CNS stimulant along with psychostimulant action same as dextroamphetamine. It has same valuable effects and similar side effects in which insomnia and anorexia is most common. But the most severe problem is hypersensitivity reactions which generally involves liver (1-2% patients), and liver function test should be done in children time to time. Pemoline has slow onset of action (2-4 hrs), but has longer duration of action (8-12 hrs). It may be used a single dose or can be divided in two doses, depending on patients response. The therapy is started with a dose of 37.5-75 mg/day, and is increased by 18.75 mg/day at weekly interval till the maximal therapeutic effect of 112.5 mg/day is achieved [73]

TRICYCLIC ANTIDEPRESSANTS

Numerous reports have shown that the tricyclic antidepressants, commonly imipramine or desipramine may be beneficial for the patients of ADD. They may produce tolerance in some children and number of side effects is observed [74]. Some of the side effects can be reduced by the supreme daily dose approved by FDA (5mg/kg/day) but autonomic effects, weight loss, gastrointestinal irritation, fine tremors, hyperirritability and mood alterations persists. Also the more severe effects on the CNS (eg. Seizures) and CVS (eg. increased pulse and diastolic blood pressure) must be scrutinized. The practice of tricyclic antidepressants in ADD is limited at this point in those who are poor responders to CNS stimulants and obligatory precautions should be taken if they are used [75-76]. TCA's also stimulate phospholipase C (PLC) and the production of the second messenger inositol 1,4,5-trisphosphate (IP3). PLC activation leads to the activation of diacylglycerol (DAG) and protein kinase C (PKC) production. It is postulated that this pathway modifies the activity of glutamatergic neurons. Side effects of TCA use in children can be substantial and include dry mouth, constipation, decreased appetite, fatigue, headaches, abdominal discomfort, dizziness, insomnia and increased blood pressure. TCA's should not be used concurrently with MAO inhibitors [77].

Desipramine

is the furthermost studied and the most popular TCA used for ADHD. It considerably improves behaviour in doses ranging from 1–3.5 mg/kg/day. The most serious side effect of desipramine and other TCA's is cardiotoxicity, most ordinarily presenting as sinus tachycardia. It is recommended that children receive an electrocardiogram (ECG) before administration of TCA's, as well as before dose changes [78]

Bupriopion

is an antidepressant medication that is used as a second line treatment for ADHD. It affects the noradrenergic and dopaminergic systems and has been shown to ameliorate the symptoms of ADHD.

Bupropion has greater efficacy than Pemoline and clonidine but is not as effective as methylphenidate or dextroamphetamine. Bupropion is given in a daily dosage range of 50-300 mg (3.0 to 6.0 mg/kg/day) as Wellbutrin, although several formulations are available. Side effects include seizure activity in 0.1% of patients prescribed with dosages under 300 mg/day. The risk of seizures are reduced if bupropion is taken in doses over 8 hours apart, medication is slowly titrated upward in dose, sustained release (SR) formulation is used, and the regular formulation is not administered in high doses. Bupropion is contraindicated in patients with epilepsy or eating disorders. Drug interactions are minimal and it does not lead to cardiac conduction delays [79].

ANTIHYPERTENSIVE AGENTS/ ALPHA2 AGONIST

Clonidine and guanfacine have been shown to be slightly effective in the management of ADHD. They are central acting alpha2adrenergic receptor agonists and bind to the presynaptic terminal to produce inhibition of adenylatecyclase and a consequent decrease in cAMP formation. This results in inhibition of noradrenaline (NA) and acetylcholine (Ach) release. Clonidine has a dose range of 0.05 mg/day to 0.3 mg/day while guanfacine's dose range is between 0.5 mg/day and 3.2mg/day [80]. Side effects are usually limited and may include sedation, hypotension, headache, dizziness, stomach-ache, nausea, depression and cardiac arrhythmias [81]. Patients should have their blood pressure, pulse, liver function tests and ECG closely monitored [82]. Contraindications contain use with other antihypertensive drugs such as beta blockers. Also, the drugs should not be tersely discontinued due to risk of rebound hypertension [83].

ANTIPSYCHOTIC AGENTS

Several types of other drugs have been used for the management of ADD but are inappropriate psychostimulant therapy. Many psychostimulant drugs like chlorpromazine, thioridazine, haloperidol and reserpine are used. Chlorpromazine has been found to be effective for the treatment of hyperactivity as compared to placebo and has equal efficacy to that of dextroamphetamine, that is usually effective in about 55-70% of patients. It has wide spectrum in ADD as it is able to control hyperactivity but is unable to have significant attention improvement [84]. Low-dose of haloperidol (0.025 mg/kg) and methylphenidate both show same improvement in cognitive performance, whereas, at higher doses of haloperidol (0.05mg/kg) there is a degradation of performance [85]. Reserpine is found to produce effect in only 34% of patients and this limited success makes it unsuitable for the use. So, antipsychotic agents can be used in the treatment of ADD but they cause depression of higher CNS functions like attention and cognition. The antipsychotics are mainly used as prime agent due to extra pyramidal side effect. It is alternative for the patients which show a poor response to psycho stimulant agents [86].

NEW DRUG (ATOMOXETINE)

Atomoxetine is the first non-stimulant drug appropriate for use in children, adolescents and adults, for the treatment of ADHD [87]. The American Academy of Child and Adolescent Psychiatry recently approved Atomoxetine as a first line treatment for ADHD [88]. Its mechanism of action is the selective inhibition of noradrenalin reuptake through inhibition of the presynaptic NA transporter. Atomoxetine has a low affinity for various receptors, such as cholinergic, serotonergic, adrenergic, and histaminic. The suggested dose is 1.2 mg/kg/day in children and adolescents weighing less than 70 kg and 80mg/day for children, adolescents and adults weighing over 70kg. A single daily dose provides continuous symptom relief throughout the day. Clinical trials have revealed Atomoxetine is safe and well tolerated in the short term but studies examining long term use are unavailable [89]. Adverse effects compriseof appetite loss, stomach ache, headache and nausea. These effects are mostly mild and temporary in nature. Modest increases in heart rate and blood pressure were also reported but steadily decreased after cessation of treatment [90].

CONCLUSION

This review indicates a wide range of very effective pharmacological treatments are currently available for the management of the disorder. Stimulants such as methylphenidate have proven very capable first line medications for ADHD treatment and are supported by a number of other pharmacological options. Atomoxetine provides a novel non-stimulant ADHD treatment

for all ages. Based on data indicating that the majority of children who do not respond to one stimulant will respond to an alternate one. If one stimulant does not work at the highest feasible dose, the physician should recommend another. There are a number of useful alternatives for children with ADHD who fail to respond to methylphenidate and amphetamines. While pemoline, the remaining stimulant, has lost popularity because of its link to hepatotoxicity, the use of non-stimulant medications as second line therapies continues to increase. Clonidine, antidepressants (SSRI), antipsychotic, anxiolytics and newer agent atomoxetine may provide significant benefit as an alternative to stimulants in children who are refractory to or are unable to tolerate them, or as combination therapy in children with co morbidities.

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