Behavioural side Effects of Methyl Phenidate and Atomoxetine

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INTRODUCTION

Attention - Deficit Hyperactivity Disorder (ADHD) is one of the most common childhood behavioral disorders diagnosed in the psychiatry outdoor setting, affecting 5-7% of school - aged children^[1]. It is a neuro - developmental disorder that runs a chronic course and causes significant impairments across various domains of day to day functioning. The symptoms of ADHD are divided into two predominant categories: inattention and hyperactivity/impulsivity. Inattention is divided in two subtypes i.e. focused and sustained/ Executive dysfunction.

Pharmacotherapy plays a pivotal role in management of ADHD nowadays which effectively improves the core ADHD symptoms as well as works synergistically with non- pharmacological

interventions; thereby improving the quality of life (QOL). Stimulants i.e. Methylphenidate, Amphetamine were considered drug of choice in ADHD; but due to high side effect burden and non- tolerability focus has been shifted to other non-stimulant medication especially Atomoxetine.

Both methylphenidate and atomoxetine have various side effects. Most noteworthy of them is behavioral side effects which are relatively common but improperly or scarcely delineated in literature. The purpose of this review is to attempt to establish the various behavioral toxicities commonly encountered during ADHD pharmacotherapy; especially with Methylphenidate and Atomoxetine and their management in clinical setting.

NEUROBIOLOGY OF ADHD :

ADHD : Core Symptoms Hypothetically Linked to Malfunctioning Prefrontal Cortex

FIG 1 : NEUROBIOLOGY OF ADHD

METHYL PHENIDATE

Methylphenidate (MPH), synthesized in 1944 and patented in 1954, was first used in 1955 for a number of indications like chronic fatigue, lethargic and depressive states, including those associated with tranquilizing agents, narcolepsy along with being the drug of choice for ADHD.^[2]

Methylphenidate has been classified as a Stimulant Drug, mechanism of action being mainly increasing the DA and NE concentration in prefrontal cortex by blocking Dopamine Transporter (DAT) & Norepinephrine Transporter (NET). Oral administration of clinically approved doses of the stimulant methylphenidate blocks the transporters for both Norepinephrine and Dopamine (NET and DAT) and increases the Dopamine and Norepinephrine in the Pre Frontal Cortex (PFC) which augments downstream signal transmission thereby ameliorating various core symptoms of ADHD.^[3,4]

BEHAVIORAL SIDE EFFECTS OF METHYL PHENIDATE :

Stimulant medications like MPH are like dual edged sword; at one hand it helps to reduce the behavioral symptoms of ADHD by improving neuro regulation at various areas of PFC, but can aggravate behavioural disturbances on the other. Broadly the behavioral symptoms of MPH can be divided into two types i.e. acute intoxication and symptoms on regular use.

ACUTE INTOXICATION :

Acute MPH poisoning produces effects similar to other stimulants like amphetamine. Reports of psychiatric symptoms occurring due to MPH intoxication were euphoria, confusion, delirium, vivid hallucinations, toxic psychosis etc.^[5] Psychosis is mostly reported by those people who used to abuse the drug in runs.^[6]

There is scarcity of literature regarding behavioural side effects of MPH abuse; mostly they were limited

to case series or case reports. The presentation of this psychiatric manifestations were quite dramatic but transient. In low doses; mostly extreme anger, aggressive behavior, impulsivity were the key scenario but in high doses delirium, confusion, psychosis, panic states and hallucinations can occur^[7] MPH when abused can be more potent than amphetamines.

SYMPTOMS ON REGULAR USE :

1. PARADOXICAL HYPERACTIVITY :

This is a relatively common side effect of MPH mostly seen in the initial weeks following initiation of medication. The patient becomes more restless, agitated, and impulsive than before. Mostly seen in mentally retarded patients or with other pre existing co morbid psychopathology. It is usually associated with baseline higher dosage of MPH, rapid escalation of dose, rebound of symptoms mostly seen with Immediate Release [IR] preparation of MPH or presence of concurrent infections. To ameliorate, first any co morbid psychopathology which can lead to exacerbation of symptoms should be excluded. A 'Start Low Go Slow' approach is always beneficial. Sustained Release [SR] preparation of MPH is useful in many such scenarios where rebound of symptoms due to IR preparation is the reason of hyperactivity. If the condition persists or deteriorates despite the aforementioned measures, switching to another drug preferably non stimulant, psychological intervention including behavior therapy would suffice in most of the cases.

2. DYSPHORIA :

This is also a common behavioural alteration seen with MPH usage. The affected child becomes sad, irritable, fatigued with less interest in daily activities. Usually there is a temporal association between emergence of the dysphoria with the initiation of MPH use. It is mostly associated with using higher dose than recommended or rapid increase in dose. Presence of depressive disorder is to be excluded in such cases.^[8]

3. PSYCHOSIS :

Although relatively uncommon, numerous case reports regarding emergence of psychotic symptoms after MPH use are available. These can be new onset psychotic symptoms or unmasking of pre existing psychotic symptoms. It can range from simple fearfulness, sleep disturbance, delusion, hallucination to full blown psychotic symptoms like that of mania, schizophrenia or schizophreniform psychosis. Many a times the emergence of florid psychotic symptoms along with exacerbation of irritability, anger outburst, decreased need for sleep points towards unmasking of bipolarity which is very common in pediatric age group. Immediately stopping the stimulant medication, addition of antipsychotics, mood stabilizers or benzodiazepines can overcome the psychotic state.^[9,10]

4. DRUG ABUSE :

As ADHD is more accurately diagnosed and treated appropriately with stimulant medication, there will be a continued increase in the amount of methylphenidate prescribed and dispensed. Given this increasing number of patients receiving methylphenidate and the increased availability of methylphenidate, there is an increased potential for this medication to be abused. Abuse often entails the use of large doses, which may be taken intranasally or intravenously. When methylphenidate is abused, it is the stimulation of D1 dopamine receptors in the nucleus accumbens and striato-orbitofrontal cortex that is thought to be related to the euphoria and repeated use. The potential for abuse is emphasized throughout the literature and should serve as a warning to clinicians. However, this warning is often overshadowed by the many patients who have a positive therapeutic response to oral MPH and do not abuse it. When used intranasally, MPH has receptor effects similar to those of cocaine. A rapid release of synaptic dopamine occurs, producing subjective effects of an instant "high"

and an intensely gratifying euphoria. Thus, the clinical picture of abuse is often quite similar to that of cocaine. Volkow and colleagues have found that the localization of MPH binding with dopaminergic pathways was "identical" with that of cocaine and a similar "high" was described by patients receiving both drugs intravenously. The sole source of MPH for these patients involved the diversion of prescription medication in most of the cases.^[11, 12]

5. TICS :

A tic is a sudden, repetitive, nonrhythmic motor movement or vocalization involving discrete muscle groups. Relatively common side effect with MPH. It is most commonly seen in patients who have family history of Tic disorder, already suffering from Tourette's syndrome, mentally retarded child etc. According to various sources of literature, MPH can only unfold or exacerbate pre existing tics; but do not cause it to happen de novo. It has nothing to do with the type of psycho stimulant, formulation or duration of use. Motor tics are more common than vocal. While managing MPH induced tics, risk-benefit assessment has a pivotal importance because many a times Tics have its own waxing- waning course which may confuse or complicate the clinical scenario. Adequate reassurance, psycho educations are important pre requisites. If the Tics do not reduce over a period of 2-3 months; reduction of MPH dose, changing to a non stimulant medication, adding low dose anti psychotic like Risperidone or Haloperidol, or using non pharmacological management are the mainstay of therapy.^[13]

6. OCD :

This is a relatively uncommon and rare side effect of MPH. Literature is scanty except a handful of case reports. Mostly seen after 2-3 weeks of treatment with MPH especially after a dose hiking. Any types of obsessive or compulsive symptoms can occur, though repetitive cleaning, arranging were most common. Most of these

cases were associated with Tics implying common neurobiological underpinning of these two disorders. Management includes discontinuation of MPH, addition of another stimulant or non stimulant like Atomoxetine, non pharmacological management or addition of SSRI with MPH.^[14]

7. BODY FOCUSED REPETITIVE BEHAVIOUR :

Like OCD, MPH induced Body Focused Repetitive Behaviour is very rare entity with only few case reports are available. The existing literature mostly delineated skin picking disorder [Dermatillomania] and hair pulling disorder [Trichotillomania] in context with MPH use. No causative association could be established though. Management includes reduction of the dose of MPH, psychotherapy especially Habit Reversal Training, changing to another class of medication or using SSRI.^[15]

ATOMOXETINE

Atomoxetine is a Selective Norepinephrine Reuptake Inhibitor [SNRI], commonly used for ADHD as well as an augmenting agent in treatment resistant depression. It specifically blocks NE reuptake pump thereby inhibiting NE reuptake; thus increasing NE concentration in the synaptic cleft and improves downstream neuronal transmission. It predominantly acts at PFC. Due to inhibition of NE reuptake, concentration of DA neurotransmission also increases at PFC thus improving the cardinal features of ADHD.

BEHAVIOURAL SIDE EFFECTS OF ATOMOXETINE :

Like MPH, Atomoxetine, despite being a non stimulant, have side effects that adversely affect the behavior pattern. Though incidence is relatively lesser than stimulant medications; some of the features are worth mentioning.

1. SUICIDAL BEHAVIOUR :

This is a very alarming side effect with Atomoxetine which mimics that of SSRI. Actually during the initiation of Atomoxetine therapy, accumulated NE in the synaptic cleft specifically acts on pre synaptic auto receptors at somato-dendritic end thereby inhibiting downstream neurotransmission. It may lead to dysphoria, mood lability, irritability, impulsivity and risk taking or suicidal behavior. It usually takes place in the initial few weeks of medication. After that, when continued NE stimulation desensitizes the pre synaptic auto receptors, downstream NE neurotransmission begins thereby heralding the therapeutic benefit. So, before giving the medication proper reassurance and knowledge about such adverse effect is a necessary pre requisite. If the situation is beyond control, urgent hospitalization, high risk management, stopping Atomoxetine and switching to other medication group for ADHD, addition of low dose anti psychotic or benzodiazepines are the available options for management.^[16]

2. PSYCHOSIS :

Like SSRI, Atomoxetine can induce manic switch in patients having underlying bipolarity. It can theoretically exacerbate psychosis as it increases DA neurotransmission in PFC. In such scenario, stopping the medication, revising the diagnosis, adding an antipsychotic or mood stabilizer are the feasible options for management.^[17]

CONCLUSION

Both MPH and Atomoxetine are considered as mainstay of pharmacological management of ADHD nowadays. Despite their clinical efficacy, presence of various side effects complicate the clinical picture many a times leading to non compliance with compromised quality of life. Behavioral side effects of both these drugs especially MPH are worth mentioning as they are quite confusing because most of the times they overlap with the core clinical

pictures of ADHD. A high degree of suspicion, evaluation of co morbid psychiatric disorders, lower baseline dose with gradual escalation, consideration of alternative pharmacological and non pharmacological treatment options are necessary to combat such behavioral toxicities.

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