

Psychopharmacology for Behavior Problems in Children

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One of the noteworthy aspects of the August 1969 issue of *Indian Pediatrics* was that it contained the first double-blind randomized study to be published in the journal since its inception. This study [1] entitled 'Hydroxyzine hydrochloride in the management of children with behavioral problems' originated from the departments of Pediatrics and Psychiatry at Amritsar Medical College. This was the natural progression of scientific curiosity due to two studies conducted earlier in the same departments. One had identified psychological disorders in 800 children presenting to the child guidance clinic with behavioral issues and the other had observed behavioral problems in 1000 children admitted with acute illnesses.

Psychopharmacology is the field concerned with clinical benefits of psychotropic drugs, their characteristics that predict responsiveness, side effects, toxicity, and the interactions between drug and psychological variables. In this write-up, we will discuss the journey of psychopharmacology, including hydroxyzine, and its current status.

THE PAST

Historical background and past knowledge: During the early to mid 20th century, society and the medical world in the West considered a model child as one who could self-regulate behavior and maintain orderly social relations. In contrast, a 'problem child' displayed a broad range of misbehaviors. According to severity of the problem, these children were managed with psychotherapy and medication in outpatient clinics or residential institutions (primarily meant for neurological diseases) [2]. In those days, several discoveries of psychotropic drugs for pediatric use were serendipitous. In 1937, a psychiatrist George Bradley studied the effect of Benzedrine sulphate, an amphetamine, on 30 children with behavioral problems at the Bradley Home for 'problem children' in America, and reported a

striking improvement in 50% [3]. This paved the way for empirical experimentation with other drugs. Several studies between 1957 and 1963 reported benefits in behavior with hydroxyzine [2,4]. Stimulants started being used for 'minimal brain dysfunction' and antidepressants for enuresis. By the 1970's, research methodology had evolved with placebo-controlled, double-blind studies. When scientific research demonstrated a dramatic response to stimulants in Attention Deficit Hyper-activity Disorder (ADHD), it heralded the start of the era of evidence-based use of drugs in mental health illnesses in children.

The study: This differed from previous studies by examining the effect of hydroxyzine hydrochloride on various categories of behavior. Authors enrolled 100 children consecutively

presenting to their child guidance clinic with behavioral issues, and conducted their baseline clinical and psychological assessment. Eligible participants were randomly assigned into two groups: group I received hydroxyzine (25-50 mg twice a day) for six weeks followed by a placebo for the following six weeks; and the sequence of drug administration was reversed in group II. Placebo and hydroxyzine liquid formulations were dispensed in identical bottles that were coded. Each child was followed-up weekly for parental reports about change in behavior (scored on a Likert scale ranging from -1 for worse to 4 for recovery) and side effects. Blood counts, kidney function tests and urine examination were performed at baseline and on completion.

The age range of the study population was 0 to 14 years with a 2:1 boy-girl ratio. Underlying causes were organic in 39% and psychogenic in 61%. Symptoms were categorized into 10 clusters that pertained to: food intake ($n=29$), sleep ($n=19$), speech ($n=10$), motor behavior ($n=22$), body manipulation ($n=8$), sex behavior ($n=2$), emotional behavior ($n=77$), psychosomatic ($n=40$), social behavior ($n=40$) and hysterical behavior ($n=2$). In



children with multiple symptoms (that ranged from 1 to 9), a mean score was computed for each child, by dividing the sum of scores by the number of behaviors.

It was observed that group I (Hydroxyzine vs placebo) showed improvement in 82.5% initially, which was maintained in 77.6% in the second phase. In contrast, only 24.3% of group II (placebo → Hydroxyzine) showed improvement initially that increased to 88% after the switch-over. Overall improvement was seen in 83% (complete 29%, marked 36% and moderate 18%). Significant improvement was noted in all behavior clusters except speech disorders, body manipulation and social behavior. Side effects were observed in 10% that were mild, and did not warrant discontinuation of drug. The authors recommended hydroxyzine for all behaviors except the three in which no change was seen.

THE PRESENT

Behavior problems in children are increasingly being recognized, including in organic disorders such as epilepsy [5] and cancer [6]. Maladaptive behaviors are behaviors severe enough to impair activities of daily living. Behaviors in typically developing children usually benefit from counseling with avoidance of inadvertent parental reinforcement. Those that satisfy the diagnostic criteria of a mental health disorder require individualized behavioral modification therapy and possibly psychoactive drugs that affect mood, thinking, and/or behavior.

Research in psychopharmacology has made quantum leaps in the last 50 years. We know that psychoactive drugs interact with specific target sites or receptors in the central nervous system (CNS) by primarily acting on neurotransmitters. In addition, they may alter the secretion of hormones, especially from the pituitary. These drugs may be considered for cognitive, emotional, and/or behavior symptoms when there is no response to evidence-based, non-drug therapies (provided by psychologists, social workers and counsellors), significant distress, functional impairment or risk of harm. Commonly encountered target symptoms include agitation, aggression, anxiety, depression, hyperactivity, inattention, impulsivity, mania and psychosis. The main classes of drugs in use are typical and atypical antipsychotic drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), stimulants and anti-anxiety drugs. The choice of drug depends on the predominant behavior and/or the underlying disorder. Stimulant medications are useful for inattention and hyperactivity; antipsychotic medications for marked irritability, and tranquilizers target aggression and mood stabilization. Long-acting stimulants are being used in ADHD, antidepressants for depression and anxiety disorders, antipsychotics for conduct

disorders, and SSRIs for autism spectrum disorder, obsessive-compulsive disorder, Tourette's disorder and motor tic disorders. To ensure safe and appropriate use, best practice principles of prescription should be followed [7]. This involves assessment, planning treatment and monitoring, obtaining assent/consent, implementing treatment, and monitoring the patient for adverse effects (especially for obesity and metabolic syndrome).

It is now known that hydroxyzine affects the CNS by reducing production of a proinflammatory cytokine, selective serotonin reuptake inhibition and increasing GABA levels [8]. This decreases anxiety and improves behavior. Current indications include pre-procedural sedation, generalized anxiety disorder, bruxism and sleep problems (especially in hepatic encephalopathy due to cirrhosis) [9,10]. With emerging evidence of its anti-inflammatory and immunomodulatory actions and lack of long-term side effects, there is a renewed interest in the treatment of neurodevelopmental disorders like Autism spectrum disorder [8]. A tale of hydroxyzine in behavioral symptoms of children that started 50 years ago has come full circle and finally made its way back.

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