Psychopharmacology Update:

Pediatric Psychopharmacology Update: Psychostimulants and Tics – Past, Present and Future

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For over three decades, there has been an intriguing association between transient tics, tic disorders and ADHD. One of the most compelling findings is that about half of the children with Tourette's syndrome also have ADHD (Allen et al., 2005). In addition, a history of tic disorders or transient tics has been observed in approximately 27% of children with ADHD (Gualtieri and Patterson, 1986). For comparison, Zahner and colleagues (1988) noted that approximately 5 -18% of boys and 1 - 11% of girls present with tics, twitches, or habit spasms at some point in their lives.

In fact, the highest incidence of tic disorders is observed in those between the ages of 7 and 13 years. However, several children are also initiated on psychostimulant medications around this age range. This article reviews the literature and examines the association between psychostimulant use and the emergence and/or exacerbation of tics.

Denckla (1976) was one of the first to document an association between stimulant use and tics in a study of 1,520 subjects diagnosed with 'Minimal Brain Dysfunction' (now called Attention Deficit Hyperactivity Disorder (ADHD)). In this study, Denckla found that approximately 1% of children, none of whom had a history of a tic disorder, experienced tics when prescribed MPH. Of those with a pre-existing tic disorder, approximately 13% (6 of 45 children) had an exacerbation of their tics. Furthermore, the tics either improved or disappeared in 13 of the 20 children (65%) when the stimulant was discontinued. Denckla's observations were later confirmed by Lowe in 1982 when she published a similar report of precipitating motor and vocal tics in children having a positive family history and receiving MPH. Resultant to studies such as these, many clinicians suggested that the use of MPH be avoided in those with a current or family history of tic disorders (Castellanos, 1999; Mick, 1996; Varley 2001).

By 1986, three more case reports regarding the association of tics with psychostimulants were published (Erenberg, 1985; Casat, 1986; Gualtieri, 1986). These reports added to the literature by demonstrating that the motor and vocal tics, which emerged after MPH administration, were effectively treated with other medications commonly used for tic disorders (such as thioridazine, haloperidol, or clonidine). These authors, however, commented that the data available at that time was insufficient to confirm whether stimulants directly caused tics and suggested that larger scale clinical trials would be required.

By 1999, our understanding of tics and their correlation with psychostimulant use at various dosages had somewhat improved. Castellanos and colleagues (1999) conducted a nine week, placebo controlled, double-blind crossover study to determine the effects of stimulant use on tic severity in 20 patients with Tourette's syndrome and comorbid ADHD. They compared the rates of tics observed at various dosages of MPH (means were 0.43, 0.67, and 1.20 mg/kg BID), DEX (means were 0.2, 0.41, and 0.64 mg/kg BID) and placebo. At lower doses (e.g., 15 mg BID for MPH) tics in the study group were, on average, not worsened by either stimulant. At higher doses however, there was a significant increase in mean tic severity for both medications (21% increase for MPH and 25% increase for DEX) compared to placebo. For those receiving MPH, tic severity for the majority returned to placebo levels within 1 to 3 weeks while only one child receiving DEX had a decline in tic severity. It is important to note that individually, some children did have worsening tics while others noted an improvement.

Law and Schachar (1999) conducted a double blind (DB) randomized control trial (RCT)

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to study the effects of MPH in 91 children with ADHD, with and without comorbid tic disorders (note: patients with severe tics and Tourette's syndrome were excluded). Contrary to some of the previous studies, Law and colleagues concluded that there were no significant differences in tic frequency between those in the MPH group (at doses of 0.5mg/kg BID) and the placebo group in children with or without preexisting tic disorders.

Gadow and colleagues (1999) studied the effects of MPH in 34 children with chronic multiple tic disorder. The primary purpose of this study was to determine whether tic frequency and/or severity would increase after long term use of MPH. Frequency and severity were measured using the Yale Global Impression Tic Severity Scale (YGTSS), the Shapiro Tourette Syndrome Unified Rating Scale, and the Global Tic Rating Scale (GTRS). After an eight week, DB, placebo controlled MPH evaluation, the children were assessed every six months for two years as part of a prospective, open follow up study. The results from their data showed no evidence that motor or vocal tics were exacerbated over the long term in these children. However, when evaluating the individual data, they found considerable fluctuations in tic frequency and severity, indicating that spontaneous exacerbations of tics may naturally occur and dissipate.

In 2001, Varley and colleagues conducted a retrospective chart review in 517 individuals given a psychostimulant [MPH (n =374), DEX (n=126), MPH + DEX (n=4), or pemoline (n=13)] to determine the likelihood of tics occurring. Those with and without tics were compared with regards to their age, the duration and type of treatment. The authors reported that 8% of the subjects developed tics. Those taking MPH who developed tics were significantly younger (mean 9.9 years) than those who did not (mean 11.1 years). There were no differences found in the 2 groups receiving dextroamphetamine. In addition, those given pemoline or the combination of MPH and DEX were too few to determine whether or not there was a correlation between age and tic onset. The authors further remarked that the different stimulants show comparable frequencies of tic emergence, however; the findings may actually represent the natural onset of tics in children rather than a result of stimulant use. They failed to find any effect of dosage or duration of treatment, suggesting that "tic emergence may occur in biologically vulnerable individuals or that it may be unrelated to stimulant treatment".

Interestingly, other recent studies have not been able to confirm a causal relationship between stimulant use, dose, and the emergence of tics or exacerbation of tics in children with a tic disorder. In a small dose-response, cross over study by Stein and colleagues (2003), 47 children (aged 5 to 16 years old, mean age 9 years) with ADHD were given 18 mg, 36mg, or 54mg of OROS MPH daily. Children with Tourette's syndrome, seizure disorders, mental retardation and severe mood disorders were excluded. Approximately 5% of the children had tics emerge as "side effects". Interestingly, 2% of participants had tic disorders at the onset of the trial. The emergence of tics did not appear to be dose related, however the authors suggested that the prevalence of tics appeared to be higher in the cohort of children who were younger and lighter; however, weights of the children were not specified in this paper.

In 2004, Palumbo and colleagues pooled data from three placebo controlled trials lasting one to four weeks, and two open-label studies, one lasting nine months and the other lasting two years. The controlled trials involved a total of 416 patients, receiving OROS MPH, IR MPH or placebo. Approximately 13% of patients in each of the three groups had a history of tics and there was no significant difference between the three groups of the number of children that experienced tics. In the two year open label trial, they found that the risk of tic episodes was significantly greater in children previously diagnosed with a tic disorder but the data suggest that stimulant therapy (mainly MPH) should not be denied in children with ADHD and tic disorders.

When assessing the causative nature of tics and stimulants, we are faced with several factors to consider. First, the presence of tics is confounded by a number of variables. Since the severity and frequency of tics often waxes and wanes, it is difficult to determine whether or not they are the result of stimulant use or an underlying disorder. In patients with a preexisting tic

disorder, stimulant medications may play a part in treating ADHD. Although it is possible that children with tic disorders experience a transient worsening of tics when taking stimulants, the literature has not always confirmed that this increase is significantly more than that which would be observed with placebo. Furthermore, some children experience a decline in tic frequency and severity while taking stimulants. As well, it is possible that transient tics and tic disorders may spontaneously develop/worsen, and are not necessarily the result of taking stimulant medications.

Conclusions

To date, research has not established a "definitive and causal" relationship of the emergence of tics with stimulant use. Though some studies have indicated that transient tics may occur more often in a population of ADHD patients (with and without a history of tic disorders) treated with stimulants, this data remains controversial.

For the future, further questions that need answers include: Is there a relationship between age and weight of a child and the emergence of tics with stimulant use? As most studies are done using MPH, does changing medication in a child who has developed tics have an impact? Why is it that some children are more prone to tics than others when using stimulants? As research continues, more persuasive evidence will become available to help us understand this association.

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