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Misplaced Fear? FDA Contraindication to Psychostimulant Use in Children with Tics

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Pringsheim and Steeves conducted a systematic review of the pharmacological treatment of Attention-Deficit Hyperactivity Disorder (ADHD) in children with comorbid tics.[1] The authors synthesized the results of eight randomized, placebo-controlled trials in this population. Their work yields two important findings:

1. There is no evidence from randomized, controlled clinical trials that therapeutic doses of psychostimulant medication worsen pre-existing tics.
2. Alpha-2 agonist medications, such as clonidine and guanfacine, appear comparably effective to psychostimulant medications in treating ADHD symptoms in children with tics.

Despite some minor methodological differences, this work largely confirms the results of a similar systematic review and meta-analysis in this area.[2] These findings have important implications for both clinical care and public policy regarding the treatment of children with ADHD and comorbid tic disorders.

Implications for Public Policy

The Food and Drug Administration (FDA) currently requires the package inserts of most psychostimulant medications in the United States to list the presence of a tic disorder or a family history of Tourette's syndrome as a contraindication to their use. This warning was issued based on a large collection of case reports and case series. These case reports associated the emergence of de novo tics and exacerbation of existing tic symptoms with methylphenidate, dextroamphetamine, and pemoline. However, the association between psychostimulants and tics may be a result of confounding. Approximately 20% of children with ADHD develop a chronic tic disorder and the symptoms of ADHD typically precede the onset of tic symptoms by several years.[3] Therefore, a significant proportion of children diagnosed initially with ADHD will eventually develop tics regardless of treatment. Supporting this observation, there were several case reports, around the same time period, linking medications that are not psychostimulants (alpha-2 agonists) to tic exacerbation. [4, 5] Alpha-2 agonists are currently recommended by the Tourette Syndrome Association Medical Advisory Board as the first-line pharmacological treatment for tics. [6]

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The data supporting the FDA warning appears even thinner in light of the trial data synthesized by Pringsheim and Steeves, which suggest that there is no exacerbation of tics with methylphenidate use; in fact, , there is a trend towards improvement in tics (effect size=0.28, p=0.07).[2]

The FDA warning also has a significant effect on physician behavior. Many doctors in the US are hesitant to prescribe psychostimulants to children with tics or who have a positive family history of tics. They know that a large proportion of these children will subsequently develop tics (regardless of whether the medication is actually responsible) and the doctors may be held responsible and possibly sued for prescribing a contraindicated medication. This contraindication therefore likely leads to many children with tics being suboptimally treated for their ADHD. Untreated ADHD has significant implications for both individuals and society. When ADHD is present in children with tics, the ADHD typically causes greater impairment in academic performance and social relationships than do the tics themselves. Childhood ADHD is also associated with an increased risk of substance use and car accidents, as well as higher rates of incarceration and unemployment.

In light of the data from this review, it would be prudent for the FDA to remove the contraindication for the use of psychostimulants in children with comorbid tics (or family history of Tourette syndrome). Instead, it may be more appropriate to list tics as a possible side-effect. After all, none of this trial based data can rule out the possibility that psychostimulants may worsen tics in a small number of individual cases.

Implications for Clinicians

Pringsheim and Steeves synthesize data from several clinical trials that suggests alpha-2 agonist medication, and probably atomoxetine (a selective norepinephrine reuptake inhibitor), may be as effective as psychostimulant medication in the treatment of ADHD in subjects with comorbid tics.[1] For most individuals with ADHD and tics, alpha-2 agonist medications are a preferable first-line treatment compared to psychostimulants as they can significantly reduce symptoms for *both* conditions.[2] However, as suggested in the Tourette syndrome Study Group trial, the combination of an alpha-2 agonist *and* methylphenidate was superior to either treatment alone in children with ADHD and tics.[7] Furthermore, the combination of these medications is usually quite well tolerated.. Troublesome side effects of psychostimulants (insomnia and anxiety) are often counteracted by the side-effects of alpha-2 agonists (sedation and fatigue). Despite the current FDA warning, a psychostimulant medication could be considered the initial drug of choice when rapid symptom relief is needed in a child with ADHD and tics because improvements with psychostimulants can be seen in days while improvements with alpha-2 agonists usually take weeks. For instance, a methylphenidate derivative would be advisable, based on current data, in a child with severe ADHD and minimal tics who was in need of rapid improvement of ADHD symptoms at school (i.e. at risk of expulsion from school for disruptive and impulsive behavior).

Conclusion

Pringsheim and Steeves systematically reviewed 8 randomized controlled trials involving the pharmacological treatment of Attention-Deficit Hyperactivity Disorder (ADHD) in children with comorbid tics.[1] Existing trial literature shows that, in the vast majority of cases of children with ADHD and comorbid tics, psychostimulants improve ADHD symptoms with no evidence suggesting that they worsen tics. As new evidence emerges from randomized, placebo-controlled trials, it is likely that the association inferred from case report level data was likely subject to confounding. The FDA should reconsider its current listing of tics, or a family history of Tourette syndrome, as a contraindication to use of these medications in treating ADHD. Furthermore, clinicians should not be afraid to consider utilizing psychostimulants in children with tics and persistent ADHD symptoms, especially when other available pharmacological and behavioral treatments for ADHD have been ineffective.

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