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Hunting for ‘Woozles’ in the Hundred Acre Wood of ADHD

Myths abound in the imagination of some clinicians, just as Winnie-the-Pooh believed that Woozles—imaginary, yet feared honey stealers—exist. Consider the following excerpt from a classic children’s book.

One fine winter’s day when Piglet was brushing away the snow in front of his house he happened to look up, and there was Winnie-the-Pooh. Pooh was walking round and round in a circle, thinking of something else...

So begins the 1926 *Winnie-the-Pooh* story.¹ In this chapter, the well-meaning yellow bear, Winnie-the-Pooh, has found strange tracks in the snow, which he believes belong to a “Woozle.” Pooh follows the tracks, not realizing that he’s walking in a circle. As such, he begins to notice that the tracks have multiplied, which he interprets as evidence of several Woozles.

This “Woozle Effect” has been well described in research settings and is believed to have resulted in conclusions that are not supported by or are inconsistent with the original data, which are then propagated through successive citations, resulting in a scientific “urban legend.”²

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Throughout my training from medical school, through fellowship, and during my tenure as a faculty member, I have found myself, at times, searching for Woozles and often have joined my colleagues on these hunts. Herein, I would like to share with you 3 Woozles that have resulted in current false dogmas related to attention-deficit/hyperactivity disorder (ADHD) and stimulant psychopharmacology.

Stimulants worsen anxiety

FDA-required labeling for stimulants includes strong language noting that these drugs are “contraindicated in marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.”³ However, data from randomized controlled trials and meta-analyses consistently have failed to demonstrate this effect. Moreover, sequenced treatment trials involving adolescents with anxiety disorders and co-occurring ADHD suggest that stimulants actually could reduce anxiety symptoms.

A recent meta-analysis⁴ that evaluated nearly 2 dozen studies involving approximately 3,000 pediatric patients with ADHD reported that stimulant treatment was associated with a decreased relative risk of anxiety (relative risk: 0.86). The study also observed a dose-response relationship between stimulant dosage and anxiety (*Figure, page 6*).⁴ Although the authors note that it is possible that some individu-

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als might experience increased anxiety with stimulants, many patients could show improvement in anxiety symptoms when treated with stimulants, and the authors also advise us, as clinicians, to “consider re-challenging children with ADHD who report ... anxiety with psychostimulants, as these symptoms are much more likely to be coincidental rather than caused by psychostimulants.”⁴

More evidence of a lack of stimulant-induced anxiety comes from a large randomized controlled trial of pediatric patients (age 6 to 17) who met DSM-IV criteria for ADHD and a co-occurring anxiety disorder who were treated with methylphenidate (open-label) and then randomized to fluvoxamine or placebo for treatment of anxiety symptoms.⁵ However, in this trial >80% of the 32 medication-naïve youth improved after stimulant treatment to the point that they no longer had anxiety symptoms severe enough to be eligible for randomization to adjunctive fluvoxamine or placebo.

Stimulants are contraindicated in patients with tic disorders

The package inserts for most stimulant medications warn clinicians that stimulants are “contraindicated in patients with motor tics or with a family history or diagnosis of Tourette’s syndrome.” This is particularly concerning, especially because of the medicolegal implications of the term “contraindicated” and given that as many as 1 in 5 pediatric patients with ADHD have a tic disorder.⁶ Therefore, labels that list motor tics as a contraindication to stimulant use potentially eliminate the choice of stimulant pharmacotherapy—the most effective treatment for ADHD—for a large number of patients.

When hunting for the Woozle that linked stimulants and tics and led to this language in the package insert, it is worthwhile to review a recent meta-

analysis of 22 studies (involving nearly 2,400 youths with ADHD) that suggested new-onset tics or worsening of tics to be present in 5.7% of patients receiving stimulants and in 6.5% of patients receiving placebo. In addition, in this meta-analysis the class of stimulant, dosage, treatment duration, or patient age did not seem to be associated with onset or worsening of tics.⁷

Polypharmacy represents a therapeutic failure and is not evidence-based

Although treatment guidelines generally have discouraged combination therapy for treating ADHD, there are—on the basis of efficacy—insufficient data to support this prohibition. Moreover, over the last decade, several studies have suggested benefits for combining ADHD medications that have complementary mechanisms. In this regard, 2 extended-release formulations of α_2 agonists have received FDA approval for as adjunctive treatments in pediatric patients with ADHD (extended-release guanfacine and extended-release clonidine). However, despite these FDA indications as adjunctive treatments, many clinicians remain concerned about combination therapy.

Several months ago, a large, 8-week, National Institutes of Health-sponsored trial shed more light on the use of α_2 agonist + stimulant combinations. Patients age 7 to 17 (N = 179) were randomized to (1) guanfacine + d-methylphenidate, (2) guanfacine monotherapy, or (3) d-methylphenidate monotherapy.⁸ In addition to clinical outcomes, the authors evaluated the effects of the medication on background cortical activity. Of interest, monotherapies differed between one another and the combination treatment in their effects on cortical activity. Guanfacine decreased alpha band power and methylphenidate administration was associated with an

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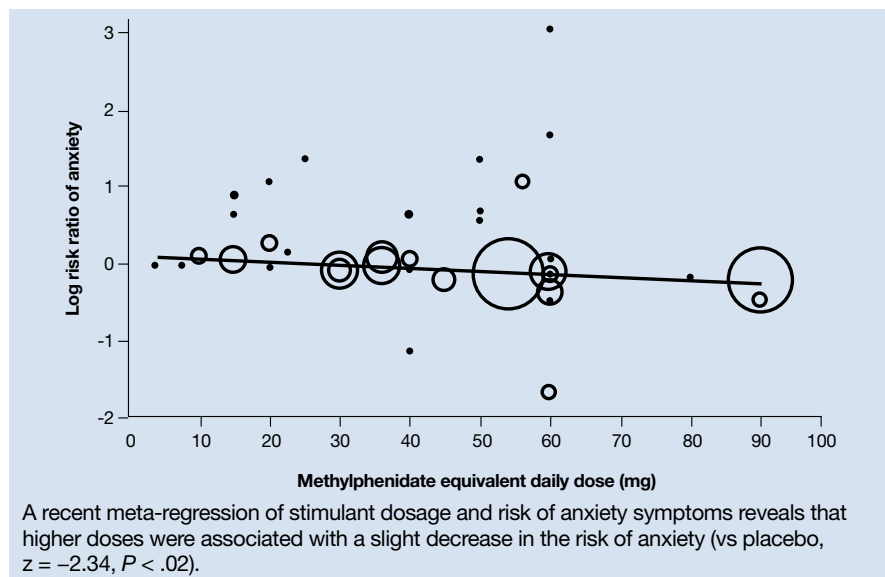


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As we evaluate evidence for our interventions, whether psychopharmacologic or psychotherapeutic, we will do well to relentlessly question the ‘evidence’ for our choices

Figure

Is stimulant use associated with anxiety symptoms?



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increase in frontal/central beta power, while combination treatment dampened theta band power and was associated with specific, focal increases in beta power.⁸ These results, although preliminary, suggest not only that medication results in changes in cortical activity that correlate with symptomatic improvement, but that combination treatment may be associated with a distinct cortical activity pattern that is more than the summation of the effects of the monotherapies. Moreover, these data raise the possibility that this synergistic effect on cortical activity may subtend—or at least—relate to the synergistic clinical effects of the 2 medications.

‘Think it over, think it under’

Having discussed several important Woozles that have inhabited the Hundred Acre Wood of ADHD for decades, it is important to remember there are countless Woozles in the larger “Thousand Acre Wood” of psychiatry and medicine. As we evaluate evidence for our interventions, whether psycho-

pharmacologic or psychotherapeutic, we will do well to relentlessly question the “evidence” for our choices and in doing so strive to be like wise Christopher Robin rather than Winnie-the-Pooh.

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