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Attention: Pediatric Advisory Committee Members
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Stimulant Treatment of ADD/ADHD
Concerns about Adverse Effects

I am a pediatrician with 25 years experience in private practice with a heavy emphasis upon common behavioral issues, including diagnosing and managing Attention-deficit hyperactivity disorder (ADHD). With a background in academic pediatrics for eleven years (1976-1987) in addition to private practice experience, I have relied upon a combination of clinical experience with an ongoing emphasis on clinical research and close scrutiny of relevant research and have published a commentary on ADHD. Increasing reports concerning adverse cardiovascular events possibly being caused by stimulant treatment, along with increasing data suggesting growing abuse and diversion as utilization continues to increase suggest that prudence dictates careful reconsideration of prevailing assumptions about safety of stimulant medications. The following considerations are offered as support for this idea.

A recent study conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA) published in *Drug and Alcohol Dependence* provides sobering data with regard to the extent to which stimulants are being abused and rates of dependence upon stimulants.¹ A summary and detailed analysis of this article is enclosed with this communication for review. Among critical findings of this study are the following:

- In 2002, an estimated 21 million persons age 12 years or older, about 9% of the population, have used stimulants nonmedically during their lifetime.
- 2.9 million have misused ADHD stimulants exclusively, representing 1.7% of the population age 12-17 years and 3.5% of those age 18-25 years.
- Three or more of seven DSM-IV criteria for stimulant dependence were found in 39,000. This included 11,000 *ADHD-specific* stimulant misusers who became dependent.

One can calculate from data provided that some 27.6% of exclusive ADHD-specific stimulant misusers became dependent among those age 12-17 years, and 13.4% of those age 18-25 years. The study did not determine whether subjects were diagnosed with ADHD or not, but it is well known that the basic effects of stimulants are the same among ADHD and normal individuals. Notwithstanding published claims downplaying the risk of drug dependence among ADHD subjects, clinical experience seems to reinforce the implications of the SAMHSA findings above, as it is widely recognized that ADHD subjects regularly experience rapid and significant recurrence of their ADHD

symptoms immediately upon withdrawal. Reports of increasing percentages of individuals who are treated with stimulants remaining on their medication for ever increasing lengths of time and a veritable explosion of what is now known as adult ADD raise further concern as to the actual prevalence of this phenomenon.

Although atomoxetine (Strattera ®) is marketed as a “nonstimulant” medication, it is in fact a stimulant every bit as much as the traditional stimulants, as evidenced by even a cursory consideration of its pharmacological action, and evidenced by the fact that it is classified as such by the World Health Organization (see enclosed).² As stated on the Strattera package insert from Eli Lilly, the mechanism by which the drug produces its therapeutic effects in ADHD “is thought to be related to selective inhibition of the pre-synaptic norepinephrine transporter.”³ Further data from the same package insert include the following:

- At the final study visit before drug discontinuation, 3.6% of treated subjects had experienced increases of heart rate of 25 beats per minute or more, and a heart rate of 110 beats/minute, compared with 0.5% of placebo subjects.
- Elevated systolic blood pressures were measured on two or more occasions in 8.6% of treated subjects compared with 3.6% of placebo subjects.

Clinical experience described among full time pediatric specialists in behavioral and developmental pediatrics in response to a question posted on a membership list-serve in May 2004 included the following:

- One respondent described encountering about 10 patients she had to be taken off Strattera because of sinus tachycardia on low doses. These subjects who experienced tachycardia had this on multiple occasions, as documented by both school nurses and by the physician.
- Another observed that she could detect a “slow metabolizer” of Strattera from observing elevated heart rate and blood pressure shortly after beginning treatment in some 7 to 10% of people.

These experiences, though not controlled, certainly support the notion that the effects of a norepinephrine reuptake inhibitor may be exactly what one would expect from this action and support the validity and common-sense wisdom of the WHO classification as a stimulant.

With the recent recognition of an increased risk of suicidal thinking and potential risk of suicide itself attributable to antidepressants, it would hardly be surprising if Strattera were found to share this risk. Under its original name, atomoxetine was tested as an antidepressant under the name of tamoxetine but withdrawn from the market due to lack of effectiveness. Recent black box warnings regarding a possible increased risk of suicide from antidepressants apply to drugs with pharmacological actions including that of being a selective norepinephrine reuptake inhibitor (SNRI). This concern has been raised in a recent report describing more than 760 spontaneous reports of cardiac disorders, 172 reports of liver damage, and some 20 reports of *completed* suicides among patients treated with Strattera.⁴ These adverse events were described in a December 9, 2005 paper sent to the Swedish Medical Products Agency by the British Medicines and Healthcare Regulatory Agency, obtained through FOIA-requests under a court order.

As a practicing clinician, I have grave concern that prevailing informed consent with regard to the use of stimulants, including methylphenidate, amphetamine, and atomoxetine products alike, fails to disclose significant risks from their use, while overstating effectiveness. As Stein has described, there are behavioral approaches that can be effective without the use of medication in many cases.⁵ Although it is usual practice to advocate behavioral treatments prior to, or combined with, use of stimulant medications, reward-based treatments similar to those advocated by Pelham, have been shown in the MTA study not to be effective when used alone. In view of the growing concerns about adverse effects of stimulants (including Strattera) as being discussed in these hearings, I submit that a trial of effective behavioral management similar to Stein's Caregivers Skills Program (CSP) should be tried *prior to* implementing pharmacological treatment. My own clinical experience has validated the potential for effective management of ADHD employing a non-disease model in which the child is motivated and encouraged to assume responsibility for self-control and self-efficacy rather than relying on external agency inherent to medication based management.

These comments are not to be construed to equate to recommending a blanket prohibition of treatment with stimulant medications, but to call for a radical revision in informed consent and for a trial of an effective behavioral approach *prior* to resorting to medication management. As use of stimulant medications continues to escalate and to be relied upon for an increasing number of years, and in the absence of long-term data on adverse effects over the number of years over which these medications are commonly used, it is unethical to begin medication treatment prior to doing so.

References

¹ Kroutil, L. A., Van Brunt, D. L., Herman-Stahl, M. A., Heller, D. C., Bray, R. M., & Penne, M. A. (Feb 14, 2006). Nonmedical use of prescription stimulants in the united states. Drug and Alcohol Dependence.

² World Health Organization. Table published online @ <http://www.whooc.no/atcddd/indexdatabase/index.php?query=N06BA09> accessed 3/6/06.

³ Eli Lilly and Company. Strattera NDA 21-411 Package Insert. (2002). Accessed @ www.strattera.com 4/26/04.

⁴ Pringle, E. (Feb 15, 2006). Strattera – 130 reports of suicidality in one month. Scoop Independent News retrieved @ <http://www.lawyersandsettlements.com/articles/strattera.html>, accessed 3/6/06.

⁵ Stein, D. (Spring, 1999). A medication-free parent management program for children diagnosed as adhd. Ethical Human Science and Services, Vol. 1, No.1, 61-79.