ADHD, Drug Labels, and the FDA: The Continuing Pre-Emption of Public Health

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Last week, two separate advisory committees of the Food and Drug Administration assembled in the suburbs of Washington to discuss the risks of existing or proposed treatments for the condition known as Attention Deficit Hyperactivity Disorder, or ADHD. Contrary to the major news reports – namely, that the FDA hearings were convened for the purpose of discussing the safety of psychostimulants – the primary objective of the FDA appears to have been the consolidation of *weaker drug labels*. As such, the recent ADHD hearings were an important test run of policy revisions which are being implemented in support of the FDA's doctrine of federal preemption.

Beginning in 2002, the FDA initiated a practice of intervening on behalf of drug companies in litigation where plaintiffs attempted to recover damages for medication-related injuries. Under the policy of *implied preemption*, the Food and Drug Administration has maintained that the very act of approving a drug and preparing its label precludes any subsequent claims by litigants at the State level. What is *preempted* is the attempt of individuals to obtain compensation for damages which arise from a manufacturer's or clinician's failure to warn about hazards associated with medical treatments.

The FDA's preemption policy provides the crucial context for understanding the timing and perceived urgency of new rules for prescription drug labeling. On January 24, 2006, the agency published revised regulations for the content and format of prescribing information. Critics have feared that these changes will weaken the ability of the FDA to demand pertinent drug product precautions (such as Black Box Warnings, contraindications, or both). Although the changes will not take effect until the end of June, their pending implementation strongly influenced the recent proceedings of the advisory committees when they considered drug treatments for ADHD.

On March 22, 2006, the Pediatric Advisory Committee minimized the severity and the drug-relatedness of psychiatric and cardiac adverse events. Although the committee recommended the preparation of a Medication Guide, describing the potential for stimulants to induce hallucinations, the members did not believe that a Black Box Warning or contraindication would be necessary. Furthermore, the committee downplayed cardiovascular events as infrequent problems occurring only in the context of pre-existing, structural heart defects. The March 23rd session of the Psychopharmacologic Drugs Advisory Committee was similarly dismissive.

Critical observers who attended the aforementioned hearings were impressed by the sham nature of the proceedings. A steady barrage of misinformation was served up by FDA officials, corporately funded academicians, and drug industry representatives. This misinformation revolved around five major themes:

Theme #1: ADHD is a serious medical condition.

Both the FDA and the pharmaceutical representatives suggested repeatedly that ADHD is a serious neurophysiological disorder. In fact, not a single textbook of neurology or pathology identifies ADHD as a medical or serious condition. The database of the National Library of Medicine lists no articles in which ADHD is cited as a cause of hospitalization, serious disability, or death.

Theme #2: Studies have shown that stimulants are the best treatment for ADHD.

On March 22nd and March 23rd, the FDA's consultant (Dr. Ben Vitiello) and a drug industry spokesman (Dr. Joseph Biederman) completely mischaracterized the results of the federal government's most important study on ADHD. When discussing the results of the MTA (Multimodal Treatment of ADHD) study, Vitiello and Biederman informed the Advisory Committees that patients treated with stimulants had demonstrated the best outcomes. This conclusion was a distortion of the relevant facts.

In a 2004 publication entitled "National Institute of Mental Health Multimodal Treatment Study of ADHD Follow-up: Changes in Effectiveness and Growth After the End of Treatment," the government research team described results according to different patient subgroups. Among the children assigned to non-drug treatment, those who remained free of stimulants achieved the most lasting improvements when they were evaluated at a two-year follow-up:

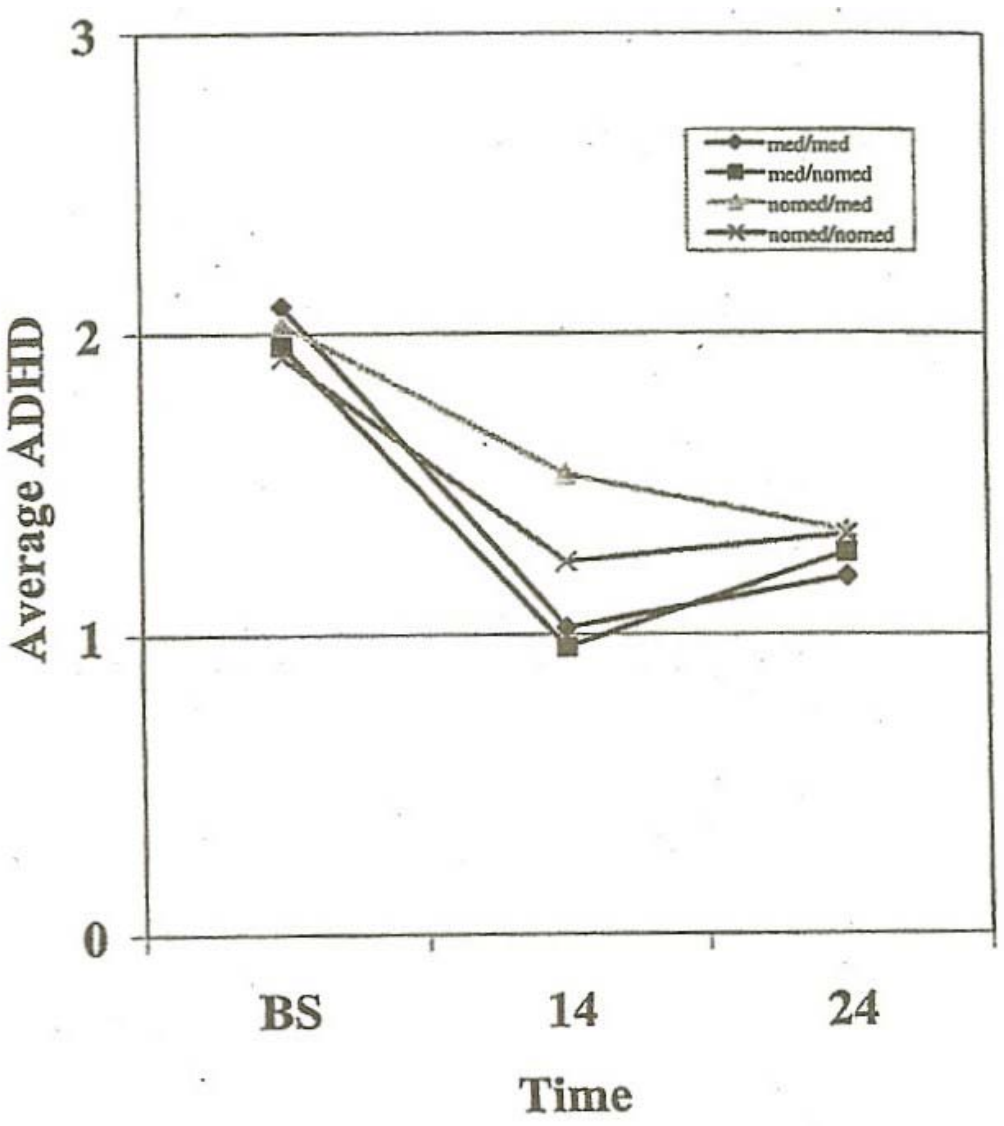
MTA Naturalistic Subgroups Based on Pattern of Medication Use

			Change in Scores 0–14 mo.	14-24 mo.
not medicated at 14 months	>	remained drug free	- 0.68	+ 0.15
medicated at 14 months	>	remained medicated	- 1.10	**+ 0.33**
not medicated at 14 months	>	added drug therapy	- 0.50	- 0.15
medicated at 14 months	>	stopped drug therapy	- 1.00	- 0.15

*the larger the negative value, the greater the symptomatic improvement
the larger the positive value, the greater the symptomatic deterioration

The table above shows that the most significant deterioration in ADHD symptoms occurred among children who received chronic therapy with stimulants. This finding is particularly impressive, when one considers the fact that the child component of the behavioral therapy intervention was limited to just one eight-week summer camp. In comparison, the children who received medication continued to receive drugs on a daily basis throughout the two-year period of care.

Reversal of Symptom Trajectories for Medicated Children by 24 Months



This graph depicts the average ADHD symptom scores over time (high scores are bad, low scores are good). By 24 months, all four subgroups converged. The subgroups are coded here according to medication status before and during the MTA study: med/med, med/no med, no med/no med, and no med/med.

Theme #3: Strattera (atomoxetine) and Sparlon (modafnil) are non-stimulants.

Throughout the two days of hearings, both the FDA and industry officials (Cephalon) repeatedly blurred the distinction between central nervous system stimulation and potential drug addiction. The FDA allowed no discussion of the criteria according to which the World Health Organization classifies atomoxetine, modafinil, and other substances as psychostimulants (those criteria being: chemical, pharmacological, and therapeutic properties).

The FDA's Acting Deputy Director for the Division of Psychiatry Products, Dr. Paul Andreason, repeatedly mischaracterized Strattera as a non-stimulant, basing this claim on his premise that the term stimulant applies only to chemicals which directly inhibit dopamine reuptake, or which directly enhance the synthesis or release of dopamine. In fact, the neuroscience literature supports the existence of many different mechanisms through which central nervous system activation (stimulation) may be achieved. Strattera, like other stimulating substances, is believed to enhance arousal, suppress appetite, and reverse narcolepsy and cataplexy by modulating the effects of norepinephrine in the frontal cortex and brainstem. Other stimulants – such as caffeine – share this property of exerting stimulant effects without directly influencing the process of dopamine reuptake or dopamine release.

A second FDA obfuscation was the claim that stimulants are defined by the potential to produce addiction. While some stimulants are associated with the development of drug liking (euphoria) and drug craving, other stimulants are not. The modification of dopamine transmission within the nucleus accumbens (so-called addiction center) of the brain is a separate issue, divorced from the criteria which are used to identify a substance as a central nervous system stimulant.

While it may seem tedious to belabor the point, the FDA's repeated failure to correctly identify atomoxetine (on March 22) and modafinil (on March 23) as psychostimulants has significant implications for product safety, since the consideration of drug risks frequently begins with an analysis of the effects which are shared by an entire class of chemicals (in this case, the stimulants). By blurring the distinction between central nervous system activation and potential addictiveness, the FDA has contributed to a fraudulent marketing scheme which has inured to the advantage of Strattera. If repeated again in the future, the FDA seems committed to aiding and abetting the same marketing fraud with Sparlon.

Theme #4: Sparlon (modafinil) has a low potential for abuse.

Although the Psychopharmacology Advisory Committee concluded its hearing with a rejection of modafinil for pediatric ADHD, the committee's deliberations were nevertheless alarming. Neither the FDA advisors, nor the FDA officials, challenged the claims of the drug sponsor (Cephalon) that modafinil carried a low potential for abuse. According to Cephalon and its spokesmen, modafinil is unlikely to be abused because its chemical properties and formulation (poor water solubility, uncrushable capsule) make it a poor candidate for intravenous injection. Unfortunately, the advisory committee and the FDA appeared to be oblivious to many important facts about stimulant abuse and addiction. First, it is not necessary to inject or snort stimulants to produce euphorigenic effects. Second, the bulk of the stimulant diversion which is now occurring on high school and college campuses relates to prescription drugs taken for cognitive or athletic enhancement, rather than for recreational ends (to get high). Third, the FDA ignored the problems of therapeutic drug dependence, stimulant sensitization (i.e., the phenomenon through which stimulants re-wire the brain in ways which make future chemical dependencies to nicotine and cocaine more likely), and incentive sensitization (i.e., the phenomenon through which stimulants, like other drugs, may create persistent feelings of drug wanting).

Theme #5: The benefits of ADHD drug treatments outweigh their potential risks.

An overall theme of the hearings was the claim that ADHD drugs must remain on the market, because ADHD is a "serious condition" for which stimulants represent the most effective intervention. Throughout the committee discussions, not a single panelist challenged the belief that the benefits of psychostimulants outweigh their potential risks.

Tragically, the FDA did not display the motivation or the knowledge essential to a competent assessment of treatment utility. In evaluating medication effectiveness (as described above), the FDA failed miserably on the job. In evaluating medication safety, the FDA did not address the many serious toxicities which have been consistently associated with stimulant therapy. For example, the FDA neglected to discuss:

- the suppression of growth (bones *and* brain)
- the impairment of cerebral blood flow (a likely contribution to cortical atrophy)
- the re-wiring of the brain (e.g., sensitizing to nicotine and cocaine)

Furthermore, the FDA completely ignored the findings of researchers in Texas, whose publications in 2005 and 2006 documented an association between methylphenidate (Ritalin) and the emergence of chromosomal damages, similar to those which enhance the risk of cancer.

From the above discussion, it will hopefully be apparent that the Food and Drug Administration is inadequate for the task of ruling on the efficacy and safety of proposed and existing treatments. Several key problems demand resolution:

The FDA does not properly characterize the identity of stimulants.

The FDA should recognize the important distinctions between central nervous system activation, peripheral nervous system activation, and the potential for addiction. These three properties are distinct and separate features of chemical entities, and the FDA should not be allowed to blur these distinctions for the sake of marketing advantages.

The FDA does not properly evaluate the safety hazards of psychiatric drugs.

It is apparent that the FDA does not appreciate the common methods which are used by neurotoxicologists to understand the real or expected hazards of psychotropic drugs. For example, the FDA seems oblivious to the fact that many psychiatric medications induce or accelerate programmed cell death, oxidative damage, and/or harmful changes in the stability of the blood brain barrier.

The FDA does not properly attribute causation to drugs when adverse events arise as a result of treatment.

The Naranjo criteria were repeatedly cited by the FDA during the recent hearings, and committee members were discouraged by FDA leaders from concluding that stimulants were a *proven cause* of serious outcomes. However, the Naranjo criteria, like other models of causation, have only limited relevance for psychoactive substances.

Naranjo Adverse Drug Reaction Criteria

adverse reaction has been reported previously
adverse reaction appeared when the drug was administered
adverse reaction improved when the drug was stopped
adverse reaction recurred when the drug was readministered
adverse reaction exhibited dose response (more severe with dose increase)
alternative causes do not explain the observed reaction
adverse reaction did not reappear when a placebo was given
drug was detected in the blood (or other fluids) in toxic concentrations
a similar reaction occurred with the same or similar drug in previous exposures
adverse reaction was confirmed by objective evidence

> The world of psychopharmacology has evolved to discuss medication effects in terms of changes in *brain anatomy* (changes in dendrites and neuronal connections) and gene expression, rather than in terms of neurochemical levels and receptor physiology. What this means is that the CDR (challenge – dechallenge – rechallenge) protocol and the investigation of dose effects may be largely inappropriate for psychiatric drugs: the removal of a medication may not lead to a timely reversal of anatomic changes induced by treatment. Similarly, the FDA should not expect a temporal clustering of adverse effects associated with psychotropics, since the timing of changes in gene expression and neuronal plasticity ("re-wiring") can vary greatly both within and between subjects. Furthermore, the FDA continuously disregards the pre-clinical and post-marketing results of laboratory and animal investigations, despite the strength of those studies in demonstrating numerous mechanisms through which psychiatric drugs exert toxic effects.

The FDA does not properly investigate or describe the problems of prescription drug dependence.

> Related to the problems described above, the FDA does not acknowledge the phenomenon of prescription drug dependence. Psychiatric patients are seldom informed about the fact that prescription chemicals can be as addictive as street drugs, from the standpoint of creating intolerable or long-lasting withdrawal syndromes when a patient interrupts or terminates treatment.

It should be obvious that the FDA's preemption policy poses a grave threat to public safety, and that this precedent must be overturned by Congressional law. It should also be noted that proposed labeling revisions may require modification [see below]. Perhaps most crucially, the FDA should be challenged about an arguable violation of the existing requirements of the Code of Federal Regulations (21 C.F.R. Part 201.57):

> "Contraindications: Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include…use of the drug in patients who, because of their particular age…have a substantial risk of being harmed by it."

Based upon the preceding evidence, the risks of stimulants *as treatments for ADHD* warrant the highest warning under federal law: a contraindication in children.

With an FDA that regularly displays incompetence and negligence in its deliberations about the efficacy and safety of medications, it cannot possibly be the case that this federal agency possesses the institutional expertise to which courts or litigants should now defer. Indeed, if the FDA is preempting anything, it is the sound practice of medicine, and the integrity of American health care.

What's Behind the Label ?

On January 24, 2006, the Food and Drug Administration finalized a new rule governing the format and content of prescription drug labeling (21 C.F.R. Part 201). Pertinent to the discussion of drug safety and the FDA's policy of federal preemption, the following changes may require modification:

Change #1: Removal of the chemical structure from the product label

Significance: Historically, the chemical structure of each drug has been prominently displayed near the top of the product label. This depiction of the spatial arrangement and molecular composition was of value to professionals in characterizing and administering the drug responsibly, because the chemical structure could be used to anticipate therapeutic effects and adverse reactions.

Change #2: Relocation of the contraindications section

Significance: A summary entitled "Highlights of Prescribing Information" has been placed at the very head of the revised product label. The hierarchy of safety information (boxed warning, contraindications, warnings, precautions) has been changed. Although a Boxed Warning section, if applied, will appear immediately and may reiterate serious hazards which appear elsewhere in the product label, the *contraindications section* has been moved. Contraindications will now follow, rather than precede, the generally lengthy descriptions about dosage and administration, and dosage forms and strength. This change *may* dilute the impact or visibility of the most essential information which can appear on a product label, for it is *only* the *contraindication* which specifically instructs a clinician to *avoid* the use of a medication in a specific group of patients or condition.

Change #3: Subtle change in guidance pertaining to "When to contraindicate"

Significance: Relative to contraindications, the new labeling provision states the following: "*Only known hazards, and not theoretical possibilities, must be listed*." The revised rule also requires that "*a causal relationship between exposure to the drug and an adverse reaction is well established*." In contrast, contraindications under the previous regulation were described with the following language: "Known hazards and not theoretical possibilities shall be listed." While the change in emphasis may be subtle (*only* known hazards *must* be listed), there is an implicit tightening of the circumstances in which the FDA will advise restrictions on the use of a drug, due to observed or expected hazards.

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