

To: Professor Kent Woods
Chief Executive
Medicines and Healthcare products Regulatory Agency – MHRA

Copy: All European Medical Agencies (concerned member states for Strattera)
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See background data in letter from January on <http://jannel.se/letter.mhra.strattera.jan08.pdf>

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The ADHD drug Strattera – an analysis of reports of drug induced mania, psychosis and hallucinations

Recently an analysis of unpublished clinical trials, buried in the archives of the regulatory agencies (FDA, MHRA), has shown that antidepressants do not work better than placebo [1, 2]. This means that pharmaceutical companies and psychiatrists with insight in the clinical trial results have told doctors and the public a false story for many years – with approval from the regulatory agencies.

This report shows *the other side* – how regulatory agencies are in the hands of pharmaceutical companies *in their postmarketing surveillance of a drug* – and how they choose to be in that position, thus misleading doctors and the public.

The case presented below gives unique insight into the “safety work” by medical agencies in Europe.

It can be assumed that the MHRA will consider this presentation to “substantially affect the policy-making process” and interfere with the assessment of Strattera by concerned member states in Europe.

This is also the main purpose with the report. Actions to protect children have been delayed for years due to the ineffective regulatory process. Doctors and parents have not been warned about the serious harmful effects of Strattera.

The other purpose is to publicly expose that the “safety work” done by medical agencies is based on analyses and conclusions from the manufacturers of the drugs – who have a strong interest in avoiding warning texts on products and other restrictive regulatory actions, and who act in that interest.

Eli Lilly’s new review of Strattera psychosis data has been said to threaten the relations between Sweden and UK – if released. Now it is.

The delay and ineffectiveness shown by the MHRA in warning parents and doctors about the treatment emergent symptoms of psychosis or mania in connection with Strattera, is described fully in an earlier [letter from January](#) – which remains unanswered.

Below is a comparison between a sharp analysis by FDA reviewers (in the Division of Drug Risk Evaluation, Office of Drug Safety) and a review by Eli Lilly, of Strattera psychosis data.

The question is posed: **Why is the MHRA using a whitewash report from Eli Lilly instead of using the already issued sharp FDA analysis of Strattera psychosis data?**

FDA researchers have, already in the end of 2005, done an analysis of the treatment emergent symptoms of psychosis or mania in connection with Strattera. Warnings were issued to doctors and parents in US as a result of this review (more below).

But the MHRA, leading the “safety work” for Strattera in Europe, did not act on this analysis. Instead the agency ordered the manufacturer, Eli Lilly, to do a review of basically the same data.

Now Lilly has completed its review and made its conclusions. And the MHRA has sent *this review* to concerned states in Europe, where medical agencies are supposed to give comments.

Let’s compare the FDA analysis with the just released Lilly review. Can we see any differences in the discussions and conclusions?

The FDA reviewers wrote:

“The most important finding of this review is that signs and symptoms of psychosis or mania, particularly hallucinations, can occur in some patients with no identifiable risk factors, at usual doses of any of the drugs currently used to treat ADHD.” (p. 3)

“For drugs currently approved for ADHD treatment, no risk factors were identified which could account for the majority of reports of psychosis-related events ... Also of note, in the overwhelming majority of cases (roughly 90% overall), the patient had no prior history of a similar condition.” (p. 4)

The conclusion was reached that the FDA review “presents compelling evidence for a likely causal association between each of these four drugs [Strattera/amphetamine drugs] and treatment emergent onset of signs and/or symptoms of psychosis or mania, notably hallucinations, in some patients.” (p. 17)

The conclusions led to changes in the **label for Strattera**. Under the heading *Emergence of New Psychotic or Manic Symptoms*, (p. 7) the following can be read:

“Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be **caused** by atomoxetine [Strattera] at usual doses. If such symptoms occur, consideration should be given to a possible causal role of atomoxetine, and discontinuation of treatment should be considered.” [3] [Emphasis here.] And this text has been in place since August 29, 2006 [3].

This is what *Eli Lilly* wrote in its new analysis:

“Assessment of the cases retrieved by the search of spontaneous [reports] was difficult because multiple comorbidities and confounders were found in the vast majority of cases, or the lack of pertinent details in other cases.” (p. 1278)

“Symptom overlap between ADHD and mania events and agitation events also make case evaluation difficult ...Attention-deficit/hyperactivity disorder as a disease state presents patients with significant symptoms and comorbidities that provide confounding factors and competing aetiology in the development of psychiatric and nervous system adverse events. The patient population would appear to be more significant in the aetiology of these psychiatric adverse events than would atomoxetine treatment.” (p. 1278)

Where FDA reviewers saw “no identifiable risk factors”, “no risk factors were identified which could account for the majority of reports of psychosis-related events”, “in the overwhelming majority of cases (roughly 90% overall), the patient had no prior history of a similar condition”, Eli Lilly saw that “multiple comorbidities and confounders were found in the vast majority of cases”, and “significant symptoms and co-morbidities that provide confounding factors and competing aetiology”.

The conclusions are diametrically opposite.

And so it goes on: FDA reviewers see compelling evidence for a likely causal association; Lilly sees difficulties, comorbidities and confounders.

FDA reviewers describe the hallucinations reported like this:

“A substantial proportion of psychosis-related cases were reported to occur in children age ten years or less, a population in which hallucinations are not common. The occurrence of such symptoms in young children may be particularly traumatic and undesirable, both to the child and the parents. The predominance in young children of hallucinations, both visual and tactile, involving insects, snakes and worms is striking, and deserves further evaluation.” (p. 3)

Lilly says on the same subject:

“Also there is uncertainty as to whether some of the events represent true hallucinations or psychotic events due to vague descriptions and the possibility that the events reported might represent other phenomena.” (p. 1278)

FDA reviewers found that the mania/psychosis resolved in many cases after the drug was stopped:

“In many patients, the events resolved after stopping the drug”. (p. 3)
[Recovery after medicine withdrawal (positive dechallenge), is an important pointer to a causal relationship.]

Lilly says on the same subject:

“Although traditionally cases with positive dechallenge are thought to provide evidence for a causal association, positive dechallenge in the case of events that maybe be episodic is of uncertain value. Agitation, hallucinations, psychosis, and mania can be episodic, and spontaneous remissions are possible in each of these events.” (p. 1276)

FDA reviewers had the following to say about Strattera and “comorbidities”:

“A psychiatric history other than ADHD was reported in 44% of cases; however, many of the stated conditions appeared to be relatively minor.” (p. 14)

Lilly says on the same subject:

“Attention-deficit/hyperactivity disorder as a disease state presents patients with significant symptoms and co-morbidities that provide confounding factors and competing aetiology in the development of psychiatric and nervous system adverse events. The patient population would appear to be more significant in the aetiology of these psychiatric adverse events than would atomoxetine treatment.” (p. 1278)

The FDA report quoted is *Psychiatric Adverse Events Associated with Drug Treatment of ADHD: Review of Postmarketing Safety Data*, released March 3, 2006.

[4] It reviewed reports submitted about mania, psychosis and hallucinations in connection with Strattera (and other ADHD drugs) up to June 2005. (It also took up aggression and suicidality in connection with these drugs.) The raw data submitted by Eli Lilly to FDA was requested by the MHRA. In August 8, 2006, Eli Lilly submitted the data to the agency. No action seems to have been taken around this material; it is not used; it is not updated.

The MHRA has clearly announced that it is NOT to make use of the analysis and conclusions from the FDA reviewers:

“Changes to European product information are based on assessment by EU regulators, agreement between members states and in line with legal

requirements about product information, not on conclusions of FDA assessors.” [5]

So what data are these EU regulators using instead when they make their assessments of Strattera psychosis data? The answer: Lilly’s review.

The Lilly report *Cumulative review of Spontaneous Case Reports of Mania, Psychotic Disorders, Hallucinations, and Agitation*, quoted above, was sent out by the MHRA to the different European countries in the beginning of February 2008. [6] In it Lilly reviews reports about mania, psychosis, hallucinations and agitation in connection with Strattera. Whereas the FDA review covered data up to June 2005, Lilly’s review covers data up to November 2007. Lilly’s review shows that there were **513 case reports about mania, psychosis or hallucinations in connection with Strattera treatment** submitted, up to November 2007.

This means that the comments from the 25 concerned member states in Europe, and in the end the conclusions from the MHRA, are based upon the analyses and conclusions by Eli Lilly in the review above.

As seen Lilly is using the following “strategy” in analysing the subject of Strattera induced psychosis: **1.** Describe the condition (in this case ADHD) as mixed with *a lot of* other psychiatric conditions (having “comorbidities”). In this way the events (as mania and hallucinations) can be seen as symptoms of *these* “disorders”, not drug induced. **2.** Take all chances to see “confounding factors” in cases. Make as much as possible out of these, so that the drug will *never* be seen to be a likely cause of the event. **3.** Describe the reported cases of mania, psychosis and hallucinations as not in actual fact mania, psychosis and hallucinations. Instead describe them as “vague” and maybe representing “other phenomena”. **4.** Invalidate all the clear cases of positive dechallenge (where the psychotic manifestations resolved when Strattera was stopped). Say that hallucinations, psychosis or mania are episodic and that it probably was a case of “spontaneous remission” (having nothing to do with the drug).

Two years after the MHRA first mentioned the need for a review of mania, psychosis, hallucinations in connection with Strattera, Lilly presents a whitewash review. After having used 30 pages to explain that the drug could have very little to do with all these harmful effects, Lilly in the end reluctantly writes: **“Nevertheless, Lilly will consider adding language regarding psychotic symptoms including hallucinations”** to its product information sheet. (p. 1279)

Having read about the need for review *two years ago*, having compared the data and conclusions in the two reviews, and knowing that Lilly’s whitewash forms the basis for the “safety work” for Strattera in Europe, it is hard to take the promise from the MHRA seriously **“...we take any necessary action to protect the public promptly if there is a problem.”** [7] It is also hard understand that this is the “safety work” for a drug that is placed on the intensive surveillance list (Black Triangle List) since long [8].

The different medical agencies in Europe seem to show little interest in the different Periodic Update Safety Reports (PSURs) on Strattera, sent out by the MHRA (based on Lilly's data and analysis). For the last three reports only two countries (Finland and Ireland) were noted as having made comments. Maybe this is not surprising, considering the flawed and biased data they have at their disposal.

Hopefully they will show more interest in doing their job after having read the above data.

Janne Larsson

Reporter – investigating psychiatry
Snöbollsgård 22
129 45 Hägersten
Sweden
janne.olv.larsson@telia.com

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