

Open letter to: Professor Kent Woods
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The ADHD drug Strattera – actions needed now

This letter gives updated information about the harmful effects of the ADHD drug Strattera. It should be of great interest to the MHRA management, considering the promise: “...we take any necessary action to protect the public promptly if there is a problem.” [1]

In this case there is *definitely* a “problem”, and it cannot have been properly communicated to the MHRA management. Shouldn't the “problem”, that there exists “**compelling evidence**” that the drug **causes serious harmful effects in many children**, have been acted upon, if the management had been aware of it?

I hope the data below will repair the lack of information and get responsible officials to investigate further and **ACT** for the safety of children.

For the years 2004-2006 there have been **31,835 adverse reactions for Strattera reported to the FDA (where Strattera was the primary suspect drug) in 9,250 individual cases (with duplicate reports excluded) [2]**. This puts Strattera as **number three** among most reported psychiatric drugs.

For the purpose of causality assessment it should definitely be observed that Strattera is in the lead – number 1 – as regards notes about positive dechallenge/rechallenge* in the reports to the FDA about psychiatric drugs:

In 1,562 unique cases – in 17% of the 9,250 cases – it was noted the subsequent disappearance of the adverse reaction(s) when medication was ceased (1,556 cases) and/or a reappearance of the adverse reaction(s) when medication was resumed (227 cases) [5]. (I suppose the MHRA finds the linked document of great value for the purpose of causality assessment. It contains highlighted data about suicidality – with 92 cases, 1/3 of the cases reported, of which could be said: When Strattera was stopped the child didn't any longer want to kill himself/herself.)

The total number of unsorted adverse reactions reported internationally for Strattera between November 2002 (when Strattera was approved) and March 2006: “During this reporting period, a total of 23,132 spontaneous adverse event reports of atomoxetine [Strattera], representing 58,048 adverse events, were collected by the MAH [Market Authorization Holder; Eli Lilly].” [6] Updating this figure with the number of reports mentioned in Periodic Safety Update Reports number 7-8, covering the periods May 2006 – May 2007, one gets a total of 61,220 adverse events in 25,034 reports for Strattera [7]. Once again: A total of 61,220 adverse events in 25,034 reports up to May 2007.

* **dechallenge**: withdrawal of a product from the patient's therapeutic regimen; **positive dechallenge**: partial or complete disappearance of an adverse event after withdrawal of the product; **rechallenge**: reintroduction of a product suspected of having caused an adverse event following a positive dechallenge; **positive rechallenge**: reoccurrence of similar signs and symptoms upon reintroduction of product. [3]

“Recovery after medicine withdrawal [dechallenge] is an important pointer to a causal relationship...recurrence on rechallenge is strongly suggestive that the medicine was responsible.” [4]

Despite “compelling evidence” for a causal association between Strattera and treatment emergent symptoms of psychosis or mania – no action by the MHRA

The word “**promptly**”, in the MHRA promise about necessary actions, refers to the manifestation of the ability of the agency to respond without delay or hesitation in case of a problem. This should be compared to ***the extreme ineffectiveness and inability to act*** described below.

In January 2006 MHRA described “a problem” of magnitude with Strattera. The agency had found out that there was a “**large number of psychiatric reactions reported**” for the drug [8]. The conclusion in the *Strattera – Risk: Benefit Assessment Report* (p. 23) was: “**Due to the large number of psychiatric reactions reported (the majority of which are unlisted), in September 2005 the MHRA requested the MAH [Market Authorization Holder] to perform a cumulative review of all psychiatric disorders reported for atomoxetine. The MAH is currently performing the review and it is anticipated that it will be available during [deleted in document].”** The **actual number of “psychiatric reactions reported” was at that time 10,988** (as stated in Annex 4 to the report) [9].

A cumulative review was however *never done*. But in March 2006 the FDA published its report over *some* of the psychiatric reactions reported from ADHD drugs, *Psychiatric Adverse Events Associated with Drug Treatment of ADHD: Review of Postmarketing Safety Data*, for the Pediatric Advisory Committee meeting, March 22, 2006 [10]. In that report it is stated that Eli Lilly (for the period January 2000 – June 2005; Strattera was approved and marketed first November 2002) had received **360 reports of psychosis or mania** (p. 14). **FDA had received 292 reports.**

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)

It is stated: “**These data show that some patients, including some with no identifiable risk factors, can develop drug-related signs or symptoms of psychosis or mania, such as hallucinations, at usual doses of these drugs.**”

It is stated: “**Positive rechallenge (i.e., recurrence of symptoms when drug is re-introduced) is considered a hallmark for causality assessment of drug-induced adverse effects. Cases which include a positive rechallenge were reported by the Sponsors for each of the drugs included in this analysis.**”

It is stated: “**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.**” And: “**The occurrence of such symptoms in young children may be particularly traumatic and undesirable, both to the child and the parents.**”

As the MHRA is well aware of, only a *fraction* of the actual adverse effects occurring are reported; it's estimated to be 1-10 percent.

The MHRA did not in any visible way act on the data in the FDA report. But the agency in some way finally found that Eli Lilly had not done or submitted the requested “cumulative review over psychiatric disorders reported for atomoxetine”, and in August 2006 the agency requested Eli Lilly to submit the same data set that, **more than one year earlier**, was submitted to the FDA and formed the basis for the FDA report (part Strattera) presented in March 2006.

Next, someone at the agency decided that no cumulative review was needed from Eli Lilly – the MHRA did neither, despite now having the necessary data, do its own analysis of the information submitted. *Nothing* was done with these data. Instead the agency wrote: **“The safety of Strattera, including review of all serious psychiatric reactions, is considered on an ongoing basis in the periodic safety update reports... Our own assessment of subsequent periodic safety updates satisfied us that the issue of psychiatric reactions could be appropriately monitored through these updates and there was not a requirement for a separate and cumulative review of psychiatric reactions with Strattera.”** [11] This was really a magic trick – suddenly the need for a full cumulative review of all the 10,988 psychiatric reactions reported had disappeared!

And so we come to **March 2007**, when, *very late*, the Periodic Safety Update Report (PSUR) for Strattera, for the period **May 27, 2005 – November 26, 2005**, was finalized. In the PSUR it is stated (p. 61) under the heading Conclusions: **“the MAH [Marketing Authorization Holder; Eli Lilly] is requested ... to perform cumulative reviews of all reported cases of hallucinations, mania, agitation, and psychotic reactions with a view to adding these to section 4.8 of the SPC [Summary of Product Characteristics] *should there be evidence of a causal association* between these events and atomoxetine treatment.”** [Emphasis added] [12]

The circle was closed. More than a year after it was stated in the *Strattera – Risk: Benefit Assessment Report* from January 2006, that a cumulative review **was needed** for the “large number of psychiatric reactions reported” (a review that was never done), the conclusion was reached **again** that a cumulative review was needed for a main part of these reactions.

The question was sent to the MHRA: How come the MHRA is not accepting the conclusions of the FDA assessors in the report presented March 2006, but instead requests *Eli Lilly* to do a cumulative review of basically the same data *already reviewed by the FDA*? And the answer was: **“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.”** [13]

All the cases of positive dechallenge/rechallenge noted for psychotic behaviour and mania in the FDA report, all the “compelling evidence” – meaning *evidence you cannot resist* – “for a likely causal association between” Strattera and “treatment emergent onset of signs and/or symptoms of psychosis or mania, notably hallucinations” – were simply neglected by the MHRA.

A later request per the Freedom of Information Act to see the “request letter” sent to Eli Lilly to get the cumulative review done is answered in the following way: **“...the responses to PSUR requests are normally submitted in a subsequent PSUR.”**

One and a half year after the “large number of psychiatric reactions” was mentioned by the MHRA as needing an urgent review, the review was still not done – and of course, no actions were taken. No warnings were issued in Europe. The “compelling evidence” for a *causal* role for Strattera in inducing psychosis or mania in children, as mentioned by the FDA assessors, was not acted upon – and, to make it even worse, the whole thing was turned back to *Eli Lilly*, the manufacturer, so that they maybe one day in the future could submit *their* analysis of the causal role of Strattera in inducing psychosis and other severe psychiatric reactions. Should we expect that Eli Lilly would find “compelling evidence” for Strattera *causing* these effects? Having read the analyses and conclusions by Eli Lilly in the PSURs I can clearly state that Lilly not one single time admits a causal role for Strattera in inducing harmful effects. Lilly will always refer to “the underlying disease”, “concomitant medication”, “confounding factors” – **even if the harmful effects are tenth of thousands there will never for Lilly be a case where the drug caused the effect!**

Can the “actions” by the MHRA, described above, be seen as an example of the principle “... we take any necessary action to protect the public promptly if there is a problem”?

And now we have arrived at the time for the publication of the *latest* Periodic Safety Update Report (number 8) for the period 27/11 2006-26/5 2007 – the 4th of December 2007. It’s two years after the MHRA published its finding about the “large number of psychiatric reactions reported” for Strattera, it’s almost two years after the FDA report was published, and it’s one and a half year after the MHRA got the full data set that the FDA report was based on.

What do we find about **hallucinations, mania and psychotic reactions** in this recently finalized report? We find on page 12 the assessor’s comment: “**The MAH has recently been asked to perform a cumulative review of all spontaneously reported cases of 1) mania, 2) psychotic disorders and 3) hallucinations.**” [7]

Still, 2 years after the original conclusion about the need for an urgent review of “the large number of psychiatric reactions” for the drug, there is no such review done – and on top of this the assessor uses the word “recently” to describe *when* the request for these key reactions was made. In the very late 5th PSUR (for the period May 27, 2005 – November 26, 2005, finalized March 2007) it was stated that a cumulative review of all cases of hallucination, mania and psychotic reactions should be done “**with a view to adding these**” to the warning section in the SPC for the drug. But with **extreme delays and ineffectiveness** the situation in present time is that no such review is done.

This means that parents and doctors in Europe *are still not told* about “the compelling evidence” for *drug induced* hallucinations and mania. They cannot find *anything* about what is mentioned in the FDA approved label for Strattera, under the heading *Emergence of New Psychotic or Manic Symptoms*, page 7: “**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 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.**” [14] [Emphasis here.] And this text has been in place since August 29, 2006 [14]. The text should be compared to the UK SPC for Strattera where **nothing** is mentioned about the fact that Strattera can **cause** hallucinations, delusional thinking, or mania [15].

It must be said that the FDA is an agency out of control, subject to Congressional investigations for its lack of ability to protect US citizens from serious harmful effects of prescription drugs. That the MHRA in this case falls far behind the FDA in ability and willingness to protect patients is probably the most scathing criticism that can be given to the agency.

The forgotten 700 cases of psychomotor hyperactivity

In an earlier letter I referred to PSUR 5 (finalized in the beginning of 2007). In that PSUR the MHRA assessors took up the subject of Movement Disorders, and included *psychomotor hyperactivity* (pages 54-55). The assessors criticize Eli Lilly and the following incredible information is given: “... **the MAH is requested to provide further clarification as to the criteria used for determining that the 700 reported cases of psychomotor hyperactivity were related to an exacerbation of the underlying ADHD which resulted in exclusion of these cases from this review.**” [12]

What could be understood from this was that Eli Lilly had received 700 reports that the company classified as reports of “*psychomotor hyperactivity*” and that these were excluded from the analysis, with the explanation that they only were a sign of “*exacerbation of the underlying ADHD*”.

This was remarkable in several ways. First of all the 700 reports would, considering the accepted rate of underreporting, represent an actual incidence of between 7000 and 70 000 cases. Secondly, accepting for a moment that ADHD is a valid medical disorder comparable to diabetes – which of course it isn't, based as it is only on subjective views, lacking any confirmable physical abnormality – this would mean that Lilly said that the “medication” (Strattera, supposed to be comparable to insulin) **worsened** the hyperactivity it was supposed to positively affect (induced more hyperactivity).

Even more serious, the effects in these cases were probably another example of misclassification by the MAH (as in the famous example where pharmaceutical companies for many years misled the medical agencies and the public about the suicide risk with antidepressant drugs – classifying suicidal behaviour as “emotional lability”, thus hiding the actual drug induced suicidality). What Eli Lilly classified as “psychomotor hyperactivity” (an exacerbation of ADHD) should most likely, in many cases, **be classified as drug induced agitation, mania or hypomania**.

The MHRA was asking *Eli Lilly* to do an analysis of these 700 reported cases, after the company had **withheld** this obviously sensitive information and classified it as “*exacerbation of the underlying ADHD*”. The natural solution should have been for the agency to request *all data* about this security risk, followed by an independent review of the data. But this was not done – **and as expected nothing is mentioned in the later PSURs – finalized December 4, about this matter. A clever guess would be that Lilly didn't provide any further clarification and that the MHRA forgot to ask – again.**

In order to help the agency with its safety work the following information can also be given:

The FDA review of psychosis or mania, aggression/hostility and suicidality was based on data up to June 2005. **The updated figures for Strattera up to December 2006 for reports about psychotic reactions/mania submitted to FDA are 340; for suicidality 378 and for aggression/hostility 688. As can be seen in the dechallenge/rechallenge summary [5] a large proportion of these reactions have disappeared after withdrawal of the drug – pointing again to the causal role of Strattera in inducing these reactions.**

Finally it should be noted that a total of **870 reported cases of suicidality and self-injurious behaviour** in connection with Strattera “treatment” have been collected internationally, up to May 2007, according to data in PSURs. And the response from the MHRA assessor in the latest PSUR (p. 22)? **“Suicide-related events are listed reactions. These reports do not raise any new issues...” [7a]** No action taken. **In other words – these harmful reactions are already known, so just continue to count!**

I would be happy to know what the MHRA management now intends to DO to protect children from these harmful effects.

Yours sincerely,

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