

Concerta for adults

Leading European Psychiatrists, Janssen-Cilag and Scientific Fraud

December 9, 2011

How could leading European psychiatrists claim that the “ADHD drug” Concerta was safe and worked fantastically well for adults, while Europe's medical agencies at the same time concluded that the drug had a “negative benefit/risk balance” and should not be prescribed to adults?

In February 2010, the pharmaceutical company Janssen-Cilag submitted its application to get Concerta approved for adults in Europe. [1] The application was accompanied by well-selected scientific evidence that would prove Concerta to be “safe and effective”.

In July 2010, the European preliminary assessment of the application was completed. In a 160-page unpublished document the findings about positive effects, adverse events and abuse potential for adults, were described in detail.

It was a devastating assessment for the pharmaceutical company. Concerta was not acceptable, it had a “negative benefit/risk balance”. It was found that the combined studies showed that Concerta had no significant benefit compared with placebo, and serious safety problems were found, including a considerable abuse potential. [2]

At the same time, leading psychiatrists, “The European Network Adult ADHD” presented its Consensus Statement on Adult ADHD. In the publication Janssen-Cilag was acknowledged for having paid all the meetings making it possible to produce the document. [3]

We will now compare what these psychiatrists had to say about the positive effects and side effects of Concerta and Ritalin (methylphenidate) for adults, in the September 3, 2010, published document, with what the European regulatory authorities concluded in their unpublished 160-page assessment of Concerta, from July 2010.

What did the leading psychiatrists say in the Consensus Statement?

The message was that psychopharmacological treatment of adults with ADHD must increase and that the document would describe what *effective treatment* meant.

And “first choice medication treatments”, they explain under the heading “Pharmacotherapy for adult ADHD in Europe”, are stimulants (methylphenidate, dexamphetamine) – “based on an extensive and still growing body of data concerning efficacy and safety”.

It is written that “Stimulants are effective in about 70% of [the adult] patients with ADHD in controlled studies”; it is referred to three studies by the now infamous psychiatrist Joseph Biederman [4].

In light of what is soon to be presented in the Assessment Report from the European regulatory authorities, the following description by these leading psychiatrists are memorable:

“Stimulant treatment not only improves the symptoms and impairing behaviours associated with ADHD, but also improves related problems such as low self-esteem, anger outbursts, mood swings, cognitive problems and social and family function. Side-effects are usually mild and transitory, mainly consisting of headache, reduced appetite, palpitations, nervousness, difficulty falling asleep, and dry mouth.”

With this almost miracle-like effect, with “mild and transitory” side effects, it is no wonder that these psychiatrists concluded the following:

“In terms of treatment, stimulants are by far the best studied and most effective treatment for ADHD across the lifespan, yet their use in some parts of Europe remains controversial in children and more widely across Europe in adults.”

The psychiatrists deplore “the lack of up to date information in their use [methylphenidate drugs], with restricted access in many European countries”.

They say that “the hesitancy and uncertainty about the appropriate [!] use [of] stimulant medication ... may also be related to the history of abuse with amphetamines in the past”. They recommend the use of methylphenidate with extended release (as Concerta) and make the following amazing statement:

“Importantly, both clinical studies and clinical experience support the view that the methylphenidate does not lead to stimulant or drug addictions. On the contrary, it has been shown to have a neutral or reducing impact on substance abuse and the risk of relapse.”

These are the words in the Consensus Statement produced in meetings sponsored by Janssen-Cilag. Now to the words from the European regulatory authorities, led by British MHRA, and what they concluded in the July 2010 assessment of Janssen-Cilag’s application about Concerta to adults in Europe. [2]

What was the view of the European regulatory authorities?

In the 160-page preliminary assessment and in final assessment document [5] a completely opposite result for Concerta was arrived at.

The assessment can be summarized as follows:

- The combined studies showed that Concerta had no significant positive effects for adults and that the drug caused a number of serious adverse effects; Concerta had “a negative benefit/risk balance” for adults;

- The pharmaceutical company had withdrawn its application about getting Concerta approved for adults;
- The submitted studies gave clear evidence that Concerta could *cause* anxiety and agitated conditions in adults (“evidence for the risk of new-onset anxiety, tension and agitation”);
- The submitted studies gave clear evidence of the considerable abuse potential and diversion risk of Concerta;
- A *causal* relationship was established for Concerta for aggression, tics, and depression;
- No warnings were to be issued about the evidence that Concerta could cause anxiety, agitated states, and aggression in adults, *for the simple reason that Concerta was not to be prescribed to adults*;
- Concerta should *only* be prescribed to adults, who before the age of 18 had been prescribed methylphenidate (Concerta, Ritalin), and who had shown “adequate response and acceptable tolerance”, *and* for which a withdrawal of the drug had been tested without success. The pharmaceutical company Janssen-Cilag declared that it agreed to the following conditions: **“those patients with ADHD who would be considered for continuation of treatment into adulthood must have previously been treated with methylphenidate and continue to show an adequate response and acceptable tolerability.”** [Note the word “must”.] No other adults could be considered.

To make it even more clear

1. The psychiatrists sponsored by Janssen-Cilag concluded in their ***Consensus Statement***: **“stimulants are by far the best studied and most effective treatment for ADHD”**. **“Stimulants are effective in about 70% of [the adult] patients with ADHD in controlled studies.”**

The European regulatory authorities concluded in their ***Assessment Report*** that the **“Benefit/Risk of Concerta in the proposed indication [for adults] is negative”**. Taken together the studies submitted by Janssens-Cilag were **“failed”**, they could not demonstrate a positive effect even short-term (after seven or thirteen weeks).

2. Consensus Statement: **“Stimulant treatment ... improves related problems such as ... outbursts of anger, mood swings ...”**

The assessment: **“A causal relationship with Concerta was established for aggression, tics and depression.”** It could be seen from submitted studies (p. 65) that **the three double-blind studies showed “13 of the 596 subjects receiving CONCERTA were withdrawn [from the studies] for aggression-related events (vs. none receiving placebo)”**.

Note the seriousness of this: 13 of the persons who received Concerta *had to be withdrawn from the studies* because of the aggression caused by the drug - *none* in the placebo group showed such serious aggression that they had to be withdrawn. In total it was reported that **71 of 596 subjects (12%) in the Concerta group had suffered from aggression** (of varying severity), compared to 5% in the placebo group.

3. Consensus Statement: **“The side effects are usually mild and transitory ...”**

The assessment (p. 66): **“The main new safety concern from the study data is around the frequency of psychiatric adverse effects and that this is often de novo [new]. Of note is the incidence of anxiety but also rates of depression and aggressive and hostile behaviour are raised.”**

“The lack of demonstrated efficacy coupled with the safety issues, especially cardiovascular safety (potential long-term effects of increase in BP [blood pressure]) abuse potential, and psychiatric/aggression AEs [Adverse Events] render the BR [Benefit/Risk] negative for the proposed indication.” (Last page, from the Dutch medical agency.)

There was a **three times higher risk for those taking Concerta in the short-term studies to suffer from manic/psychotic conditions compared with those receiving placebo** (p. 64). The harmful events leading to withdrawal from the studies **“included Thinking Abnormal (severe), Delusions of reference (severe) and Abnormal behavior (severe), and all of these events resolved following discontinuation”**. In other words, there was a *causal role* also for Concerta as regards psychotic/manic states.

4. Consensus Statement: **“Importantly, both clinical studies and clinical experience support the view that the methylphenidate does not lead to stimulant or drug addictions. On the contrary, it has been shown to have a neutral or reducing impact on substance abuse and the risk of relapse.”**

The assessment (p. 70): **“It is assessed there is a significant abuse and diversion risk with Concerta.”**

“... the misuse/abuse potential of methylphenidate is considered a major safety concern: in combination with the concerns regarding the reliability of the diagnosis, adults may try to get diagnosed for ADHD to retrieve methylphenidate in a legalised manner.” (Last page, from the Dutch medical agency.)

5. Consensus Statement: Methylphenidate (Ritalin, Concerta) is the **“first choice medication treatments”** for adults with ADHD **“based on an extensive and still growing body of data on efficacy and safety”**.

The assessment: The pharmaceutical company Janssen-Cilag has agreed to the following conditions: **“those patients with ADHD who would be considered for**

continuation of treatment into adulthood must have previously been treated with methylphenidate and continue to show an adequate response and acceptable tolerability.”

So how could these leading European psychiatrists write as they did?

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[1] Janssen-Cilag/Johnson & Johnson, *Submission for Variation Application Dossiers (s) for Concerta, ("Addition of a New Therapeutic Indication: ADHD in adults)*, 26 February 2010,

<http://jannel.se/ConcertaApplicationAdults26Feb2010.pdf>

[2] MHRA, *Preliminary Variation Assessment Report, Concerta*, July 2010

<http://jannel.se/PVAR.Concerta140710.pdf>

[3] Kooij et al, "European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD", *BMC Psychiatry*, 3 September 2010, <http://www.biomedcentral.com/1471-244X/10/67>

[4], NYT, *Researchers Fail to Reveal Full Drug Pay*, 8 June 2008,

<http://www.nytimes.com/2008/06/08/us/08conflict.html?pagewanted=all> NYT, *Research Center Tied to Drug Company*, 24 November 2008,

<http://www.nytimes.com/2008/11/25/health/25psych.html?partner=permalink&exprod=permalink>

[5] MHRA, *Final Variation Assessment Report, Concerta*, 26 May 2011,

<http://jannel.se/FVAR.Concerta260511.pdf>