The ADHD Drug Concerta Must Not be Prescribed to Adults in Europe – Janssen-Cilag gave all the Evidence of "Negative Benefit/Risk Balance"

14 November 2011

When the risks are found to exceed the possible benefit a drug must not be prescribed, "the benefit/risk balance" is said to be negative. This is what has now happened with Janssen-Cilag's ADHD drug Concerta. It cannot any longer be prescribed to adults in Europe. The pharmaceutical company itself has provided all the evidence - ironically, when applying to get Concerta approved for adults.

The amphetamine type drug Concerta (methylphenidate) has never been approved for adults in Europe. Nevertheless, it has been prescribed in large quantities, with the expectation that Janssen-Cilag will soon push through an approval. In anticipation of the "scientific evidence" psychiatrists have referred to the fuzzy concept "clinical experience". That is over now.

Even if we haven't seen any official publication about it from the European Medicines Agency (EMA) or from the national medical authorities it is decided: **the benefit/risk balance of Concerta for adults is negative, serious harmful effects have been proven, the combined studies show no significant positive effects, the drug *must* not be given to adults. The pharmaceutical company has proven or given strong signals about almost everything critics have said about this type of drug over the years.**

The scientific evidence from placebo-controlled clinical trials is available, and it says exactly the above. Concerta *has* a "negative benefit/risk balance".

What is so special here is that the manufacturer, Janssen-Cilag, unintentionally, presented the evidence forcing the medical authorities to conclude the drug has a negative benefit/risk balance. And Janssen-Cilag has really made an effort to *select* the studies which would lead to the *approval* of Concerta for adults in Europe. The company has taken the best of studies to support its application for approval.

Pharmaceutical companies' manipulations of scientific studies have led to numerous articles in medical journals in recent years, articles showing how the companies have control over the "scientific process" and that the end results are often determined already by the design of the studies. These data, more later, are also applicable in the case with the studies of Concerta to adults. **[1]**

And for those who think Concerta is a specific medicine for a specific disease, a short history lesson may be needed. The fact is that methylphenidate, the drug class to which Concerta and Ritalin belongs, has been prescribed since the 1950s. It has been prescribed to alcoholics, to persons with a diagnosis of schizophrenia, to tired housewives, depressed old people - yes the drug did really speed things up, the claimed miracle pill "cured" depression in minutes!

A brief summary - what we know about Concerta for adults today

Janssen-Cilag submitted its application to get Concerta approved *for adults* in Europe in February 2010. **[2]**

To make a long story short: The Dutch Medical Agency (CBG) summarized the situation in a good way in its assessment of the company's application, **already 30 July, 2010**. CBG wrote that it fully supported the overall assessment of the UK Medicines and Healthcare products Regulatory Agency (MHRA), **"that the B/R [Benefit/Risk] of Concerta in the proposed indication is negative".**

CBG further wrote: **"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 render the B/R negative for the proposed indication". [3]**

This was followed by requests from the authorities for additional data from the pharmaceutical company, which had not reported the results of its submitted studies correctly - it had, as expected, turned negative results in the studies into something positive. This time the UK MHRA (overall responsible for handling the application in Europe) did not accept the fraudulent presentation, and requested clarifications.

And 26 May, 2011, the investigation was completed and a final agreement was presented in an internal document. **[4]**

It 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 to get 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 abuse potential and of the risk of diversion of Concerta;

- A *causal* relationship was established for Concerta for aggression, tics, and depression;

- No warnings were to be issued about the fact that it had been proven that Concerta could cause anxiety, agitated conditions and aggression in adults, *for the simple reason that Concerta should not be prescribed to adults* ;

- Concerta could *only* be prescribed to adults who before the age of 18 had received methylphenidate (Concerta, Ritalin) and who were judged to have had an "adequate response and acceptable tolerance", *and* for which a withdrawal of the drug had been tried 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 adequate response and acceptable tolerability."** [Emphasis here.] No other adults could be considered.

What did Janssen-Cilag's "Abuse Potential Studies" show?

Among the studies submitted by Janssen-Cilag, as part of the application, were three so-called Abuse Potential Studies; studies conducted specifically to determine the abuse potential for Concerta.

One can safely say that Janssen-Cilag today regrets submitting these particular studies as evidence about no abuse potential.

The first of these studies (Study 12-005) was a double-blind, placebo-controlled study in which the subjects (N=49, 18-48 years) were "Healthy adults with a history of recreational stimulant use". Subjects had previously used cocaine (88%) and methamphetamine (25%). The study compared placebo with Ritalin (IR, Immediate Release) 60 mg and Concerta, 108 mg. It used the questionnaire Drug Rating Questionnaire, Subject (DRQS-VAS) which mainly measured the degree of Liking, as scored by a subject's response to the question: "Do you like the drug effect you are feeling now?" **[5]**

The conclusion (MHRA) was: "The results clearly suggest that even when Concerta is not crushed (a more likely scenario of abuse) that this imparts a pleasant effect in this population of recreational drug users." Ritalin IR also gave, as expected, the "pleasant effect", but there was no significant difference between the substances.

The second of these studies (Study 12-007) was a double-blind, placebo-controlled, randomized study in which the subjects (N=55) were "healthy normal adults with a history of light (occasional) stimulant drug use", in which one compared placebo with methylphenidate (IR) 50 mg and 90 mg, and Concerta 54 mg and 108 mg.

MHRA wrote that Concerta probably would be crushed if persons wanted to abuse the drug, *but* that "addiction potential" in this study also was demonstrated for the usual intake of doses (108 mg and 54 mg).

The conclusion (MHRA) was that Concerta had "a positive effect on the 'Liking elements' of the DRQS [Drug Rating Questionnaire Subject] ... If the tablets are crushed then the effects are likely to be heightened. The effect of augmentation of the effects of other drugs of misuse is not known and it is known that diversion is a significant problem".

The third of these studies (Study 12-1302) was done on *active* drug users (people with a diagnosis of "substance abuse") and part of the assessment (MHRA) was that in this group it "is unlikely that anyone would take Concerta in this fashion should they wish to abuse it". These users would, in other words, take other drugs if they had a choice, and would probably crush or take Concerta in an other way if they would just take Concerta.

In conclusion, as demonstrated by the Janssen-Cilag's submitted studies, there was a significant abuse potential for Concerta in the usual dose, 54 mg, that psychiatrists prescribe. The UK MHRA was apparently surprised by the "pleasant effect" that these "therapeutic doses" gave in the subjects. The "drug effect" that emerged made the MHRA question what the *real* outcome was all about in the other submitted, short-term studies for adults "with ADHD".

The Agency therefore finally addressed this very relevant question, and wrote about the study of Concerta, 54 mg and 108 mg: that "**pleasurable effects [had been demonstrated] which raises the question of how much the action seen in the RCTs [Randomized Controlled Trials] is due to the euphoric effects of the Concerta."**

The pharmaceutical company thus proved, with the submitted "Abuse Potential Studies", that Concerta had an abuse potential in usual doses, and even more, one got with these studies the assessing Agency to question if positive effects, as presented in the other placebo-controlled short-term studies of persons with a diagnosis of ADHD, in fact was not the familiar euphoric effect of Concerta.

As said in the final document from the UK MHRA after all the evidence was looked at:

"It is assessed there is a significant abuse and diversion risk with Concerta." [5]

And as the Dutch Agency wrote in its assessment: "… 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 way."

What did Janssen-Cilag's "clinical efficacy" studies show?

A pharmaceutical company doesn't have to demonstrate much to get an approval of a drug as Concerta for adults. They need some *short-term studies* showing that the stimulant drug has a better effect on "ADHD symptoms" (see also above on the euphoric effect) than sugar pills have, and that it does not give too serious harmful effects. The assessed "positive effects" must be greater than the potential or identified risks. With *short-term studies* are meant studies lasting only a few weeks. And the studies are done on persons who are positive to get the narcotic drug from the beginning.

Janssen-Cilag selected three studies that the company itself had designed and carried out with the aim of providing the required evidence for an application to get Concerta approved for adults in Europe.

The three studies included **a five weeks study (Study 3002), a seven weeks study (Study 02-159)** and **a thirteen weeks study (Study 3013), with a total of 899 adults "with ADHD".**

In only *one* of the studies submitted Concerta had a better *short-term* (5 weeks) positive effect on the predetermined criteria than placebo, in the other two trials one could not even *short-term* (7 or 13 weeks) get a significantly superior efficacy for Concerta compared with placebo – **"a statistically significant difference in the proportion of patients meeting predefined response criteria was not demonstrated between CONCERTA XL and placebo". [4]**

The Exclusion Criteria in the studies were extensive, as the UK MHRA noted in its report: "These were extensive and excluded any significant psychiatric or physical co-morbidity drug or alcohol abuse." A main objective was to obtain subjects who as little as possible would be likely to interfere with the positive end result.

So, for example, one *excluded* earlier "non responders" to methylphenidate, persons not considered to have had a positive effect in previous treatment with methylphenidate, or *whose children* did not have a positive effect. This was possibly appropriate, *but* one also *included* persons who previously took methylphenidate – and thought it was positive. In the first of these studies 9 percent of the subjects had earlier received methylphenidate, in the other 35 percent had got "ADHD medication" before, and in the third 8.6 percent had received treatment with methylphenidate.

It stands to reason not to include persons who already had received the drugs one is going to study, and who thought the treatment was positive, as that approach is more or less a guarantee for the end result for *this* group: Persons from this group receiving placebo notice that they did not get methylphenidate and give a negative response, persons who receive the same type of drug they previously enjoyed notice it and give a positive response. But these earlier "responders" were included; for two weeks they tapered down and discontinued their previous drugs, to then begin increasing the dose of the same type of drug again (or receive placebo).

But despite the short time for which Janssen-Cilag would demonstrate efficacy and despite the above measures to ensure a positive outcome, the pharmaceutical company could not show a "positive effect" for Concerta compared to placebo, except in the shortest of these studies, the five weeks study. *Taken together*, these studies – were failed, unsuccessful, did not demonstrate a positive effect even short-term (after seven or thirteen weeks).

And the question was also, as raised by the UK MHRA, how much of the "positive effect" which was presented, was based on the known "euphoric effect".

What harmful effects were shown in Janssen-Cilag's "clinical efficacy" studies?

As said "the benefit/risk balance" for Concerta for adults was found to be negative. The absence of positive effects in the submitted studies has been described. But what were the reported harmful effects? Consider that the harmful effects described below were shown in *short-term studies,* after only five, seven and thirteen weeks in a well-selected group of adult patients.

It emerged in the studies **[5]** clear evidence **that Concerta can *cause* aggression and hostility** in adults. MHRA said that **in the three double-blind studies 13 of the 596 subjects who received CONCERTA were *withdrawn* from the studies for aggression-related adverse events (versus none receiving placebo).**

Note the seriousness of this: 13 of the subjects who received Concerta had *to end the study* because of the aggression they got from the drug - *none* in the placebo group showed such serious aggression that they had to be withdrawn from the study.

In total **71 of 596 subjects (12%) from the Concerta group were reported to have suffered from aggression.** It should be noted that the studies excluded persons with other psychiatric problems and substance abuse problems. In the real world where Concerta is prescribed it can clearly be said that the proportion of persons affected by new or reinforced aggression is far much higher.

There was a **three times higher risk (2.9% vs. 1.0%) for those taking Concerta in these short-term studies to suffer manic/psychotic disorders compared to those receiving placebo**. The reasons persons in the Concerta group had to interrupt the studies **"included Thinking abnormal (severe), Delusions of reference (severe), and Abnormal behaviour (severe), and all of these events resolved following discontinuation".** In other words, there was a *causal relationship* between Concerta and the psychotic/manic states.

In close relation to this it was found clear evidence that Concerta can ***cause* anxiety and agitated conditions in adults** ("evidence for the risk of new-onset anxiety, tension and agitation"). **[4]**

There was also a clear correlation between the duration of the studies and how many of the subjects who discontinued the study due to adverse events. In the "longest" of the studies (Study 3013), 13 weeks, 19 percent of the subjects (34 of 182) who received Concerta discontinued because of adverse events (compared to 2 percent in the placebo group). Together with the increased harm was also an increased tendency to not want to take Concerta as directed – so called "non-compliance". 25 percent of those receiving Concerta in the highest dose (72 mg) showed "non-compliance with study medication", 22 percent of those taking Concerta 54 mg showed the same, (compared to 8 percent for the placebo group).

It was concluded from data in the presented studies: "The main new safety concern from the study data is around the frequency of psychiatric adverse events, 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." [5]

Note that these psychiatric harmful events are "de novo" [new]. They are, in other words, *caused* by Concerta, which is also what is determined by the MHRA: "A causal relationship with Concerta was established for aggression, tics and depression."

Adults who have been harmed by Concerta can now sue Janssen-Cilag and their psychiatrists for the injuries they have been caused

Janssen-Cilag have reached an agreement with the European medical authorities that they are **NOT** going to tell patients about the fact that the new studies proved that Concerta can ***cause* anxiety and agitated conditions in adults** ("evidence for the risk of new-onset anxiety, tension and agitation").

Janssen-Cilag has also reached an agreement with the European authorities that they are **NOT** going to tell patients about the fact that the new studies proved that Concerta can ***cause* aggression and depression in adults.** ("A causal relationship with Concerta was established for aggression, tics and depression.")

The reason that warnings for adults should not be issued was simply that no adult would receive Concerta!

The company explained, according to the MHRA, that **"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 adequate response and acceptable tolerability"** [emphasis here]. **[4]**

So it was – quite logical – not relevant to issue a special warning for *adults*, since these harmful effects would have shown up when the patients were under 18 years old, and they would then not be allowed to continue receiving Concerta (did not show "acceptable tolerability").

Nevertheless Janssen-Cilag has very likely hit its previous sales record from 2010 for Concerta to adults in Europe, and has for sure done it in Sweden. [6] Janssen-Cilag will thus in 2011 have sold much more of a drug the company itself and the medical authorities know have a clear negative benefit/risk balance, and it will be done without the patients in question having received the information about the known risks.

Patients who have been subjected to this fraudulent criminal behaviour, and suffered physical or mental harmful effects, should now have good opportunities to sue the pharmaceutical company and receive compensation for the harm caused.

Another chapter in this story would be how the FDA could approve this drug for adults in the US. [7]

Janne Larsson
Reporter – investigating psychiatry
Sweden
janne.olov.larsson@telia.com

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