Antidepressants for Children - Part II

Prozac for children – what happened with the follow-up?

September 21, 2010

Prozac was approved for children in Europe in 2006. **[1, 2]** Several countries were strongly opposed, but the UK and Swedish medical agencies pushed to get the drug approved. They thought it was a good idea to ***first*** approve Prozac and ***afterwards*** do the needed safety studies.

So what happened to the needed studies and the careful monitoring which were ***a requirement – a condition –*** for the approval of Prozac for children in Europe?

First read *Part I* of this sordid story, ***Prozac - how could it be approved for children in Europe?*** **http://jannel.se/prozac.childrenEU.pdf**

The Dutch Medicines Evaluation Board (CBG) was in 2005 responsible for the assessment of whether or not Prozac could be approved for children in Europe. The Agency found that Prozac could ***not*** be approved and wrote about the effects and harmful effects of the drug:

> **"In the face of the limited efficacy results, safety concerns are all the more salient. Increased risk for suicide related behaviours emerged as the most concerning safety finding from the clinical trials. Other safety concerns include effects on growth and sexual maturation including effects on fertility, and effects on cognitive and emotional development." [3]**

The Dutch agency expressed its deep disappointment with the pharmaceutical company Eli Lilly and wrote (p. 6):

> **"The responses of the company at this time... indicates that the company is not intending to carry out any more studies to address the unresolved safety concerns."**

The Agency also stated:

> **"The lack of willingness on the part of the company to carry out additional studies that would elucidate safety concerns is disappointing, as the MAH [Marketing Authorization Holder] has a clear responsibility for evaluation of safety in this population." [4]**

In *Part I* of this article I let the wise reader guess: Did Eli Lilly really in an effective way conduct the required studies, that they previously did not want to do, now when Prozac had been approved? Did the UK MHRA, the Swedish MPA and Eli Lilly after the approval start with new effective follow-up actions for the children who received Prozac?

The Swedish Medical Products Agency (MPA) had already in the early negotiations about the approval of Prozac for children pushed for such authorization. The Agency was aware of the serious signs of damage that had been presented in the case files, but said that safety issues could be investigated ***after*** the pharmaceutical company had got its positive decision:

The Agency wrote:

> "…the MPA currently supports the overall view of the UK, i.e. that approval may be recommended **provided commitments of further studies** and appropriate wording of the SPC [Summary of Product Characteristics]." [Emphasis here.]
>
> "It is a fact that SSRIs, including fluoxetine [Prozac], are used 'off label' [without being approved for what it is prescribed for] in children and adolescents, and approving use of fluoxetine allows for providing treatment recommendations, **better post marketing surveillance in these populations and possibilities to request further studies**." [Emphasis here.] **[5]**

And the English and Swedish Agencies pushed through the approval with these "scientific arguments". Prozac was approved in June 2006 and the pharmaceutical company Eli Lilly agreed to do the studies that had not been made prior to approval, and to ensure that children who received Prozac were closely monitored for effects and harmful effects.

Eli Lilly undertook at the time of approval **[6]** to do several things, which included the following:

1. Investigate the effect of Prozac on sexual maturation in children 8-12 years. This would be done in an American study ("TADSjr") under the National Institute of Mental Health (NIMH).

2. Examine if different registers in Europe could be used to obtain data on how Prozac affects the sexual maturation of children.

The company should also in Prozac studies with rats investigate the following:

4. "neurohormonal investigation of sexual maturation".

5. "characterization of testicular pathogenesis".

6. "characterization of effects on specified emotional behavior".

The Company should among other things examine what the Dutch Medicines Board had taken up about Prozac's **"effects on growth and sexual maturation including effects on fertility, and effects on cognitive and emotional development".**

We take a big step forward to 2010 and look at what happened to the proud commitments – the requirements, the conditions, for the approval of Prozac for children in Europe.

And we can in the UK electronic Medicines Compendium read:

> **"In addition, only limited evidence is available concerning long-term effect on safety in children and adolescents, including effects on growth, sexual maturation and cognitive, emotional and behavioural developments." [7]**

More than four years after the *requirements* to closely examine these long-term effects there is still "limited data" available.

So what did Eli Lilly do, and what did the regulatory agencies, who should ensure that Eli Lilly complied to the requriements, do?

Eli Lilly should first investigate the effect of Prozac on sexual maturation in children 8-12 years. This would be done in collaboration with the researchers who had conducted the TADS study, Treatment for Adolescents with Depression Study, the main study that Eli Lilly used to push through the approval of Prozac for children (see *Part I*).

The researchers who conducted TADS would with funding from the National Institute of Mental Health (NIMH) conduct a follow-up study of children 8-12 years ("TADSjr"). Eli Lilly would "catch on" and as part of this study examine the effects of Prozac on sexual maturation.

In September 2006, Lilly submitted a proposal on how to conduct the study. **[8]**
The Assessor at the UK MHRA was not satisfied and wanted several questions answered. On November 16, Lilly responsed. **[9]** The Assessor from MHRA, who apparently had decided to do a thorough job, was not at all satisfied. In the response to Lilly, on December 12, the often used phrase was "Issue not resolved" and the Assessor concluded by writing that almost none of the questions had received satisfactory answers. **[10]** On December 19, other Assessors in Europe commented on the report and a summary assessment report was issued. **[11]** On January 31, 2007, Eli Lilly replied to the Evaluators' comments and questions. **[12]** On March 1, MHRA answered on Lilly's report. **[13]** On March 12, MHRA sent a letter to Lilly to explain what was now required for this study. **[14]** And Lilly replied on April 12. **[15]** MHRA sent a report to other European regulatory agencies for comments on April 23. **[16]** Only Italy responded, and MHRA May 2, sent a new letter to Lilly and requested information. **[17]** On May 21, Lilly submitted the information. **[18]** After a few short communications Eli Lilly, July 6, submitted the revised design of the study. **[19]**

One year had now passed since Prozac was approved for children and the discussions were still about *the design of the study* that would provide answers to how Prozac affected different important aspects of children's life, including sexual maturation.
On July 19, MHRA issued a new assessment report to the European regulatory authorities. It was now agreed how the study should be done. **[20]** What remained was to actually *conduct* the study for which the design had been discussed over a year.

And this takes us forward to September 9, 2009. Now, MHRA publishes a summary of what has happened with the study that Lilly would conduct.

The Agency writes (p. 3):

> **"Now the TADS Jr study will not be conducted because of lack of funding by the NIMH, and consequently the exploration of possible effects of fluoxetine [Prozac] treatment on sexual maturation as part of this study will not be feasible."**

One of the requirements for the approval of Prozac, in June 2006, was that this study *must* be conducted. The design of the study was then discussed for a year. And now, three years afterwards, it is said that the study was not even begun – *and will not be done!*

So how do MHRA and the other regulatory agencies handle this situation?

The MHRA writes:

> **"The MAH [the manufacturer, Eli Lilly] therefore requests [as this study would not be conducted] that the post-authorisation commitment [the requirements that should be fulfilled after approval of the drug] to clinically evaluate the effect of fluoxetine on sexual maturation be considered fulfilled." [21]**

In other words, Eli Lilly requests that the requirement in this area should be considered fulfilled – *even if the company has done nothing*. The major concern about the effects of Prozac on children, that got the Dutch Medicines Evaluation Board (CBG) not to grant approval for Prozac, is existing just as much as four years earlier. Despite that Eli Lilly wants to skip all studies of long-term effects of Prozac in this area.

And what does MHRA say about this?

> **"The RMS [Reference Member State] [in this case UK] agrees that any clinical study to investigate the effects of fluoxetine on sexual maturation would be forbiddingly hard to conduct and difficult to interpret. The RMS therefore recommended accepting the Company's request that the FUM [Follow-Up Measure] to clinically evaluate the effect of fluoxetine on sexual maturation be considered fulfilled."**

Abracadabra, the requirement was conjured away. The Swedish MPA, who wanted to approve Prozac for children on the basis that there would be extensive post-marketing studies, has no real objections to the magic trick of MHRA.

And therefore, now and forever, the following will be the words in the product description for Prozac:

> **"In addition, only limited evidence is available concerning long-term effect on safety in children and adolescents, including effects on growth, sexual maturation and cognitive, emotional and behavioural developments." [7]**

No long-term studies will be conducted for the simple reason that the "responsible" medical agencies fail to request such studies.

What happened with the requirement to examine if different registers in Europe could be used to obtain data on how Prozac affects the sexual maturation of children?

No, it did not work either. According to Lilly no such suitable records were available. MHRA also accepted the Company's evaluation on this point. The Swedish Medical Products Agency did at least find something to say about it, and sent the following lame comment to MHRA and other regulatory agencies:

> **"We acknowledge these problems, however, we do to some extent question the unfeasibility of the company setting up a registry/observational study themselves." [22]** The Agency also says **"that the non-clinical FUMs [Follow-Up Measure] should be finally assessed before it is finally decided whether further clinical work is necessary."** [They use "further" even if *nothing* is done.]

Then there is the non-clinical studies in rats that Eli Lilly should conduct ("neurohormonal investigation of sexual maturation", "characterization of testicular pathogenesis", "characterization of effects on specified emotional behavior").

Well, MHRA takes up data from these studies in its final report. The Agency writes that data from these studies have not been made available as part of the assessment procedure, but says also:

> **"The MAH [the manufacturer, Eli Lilly] has conducted the required pre-clinical studies, confirming a delay in sexual maturation in rodents but apparently failing to elucidate a causal mechanism for this effect." [22]**

In other words, Eli Lilly had got proof that Prozac gives a delay in sexual maturation, but has "apparently" failed to clarify the causal mechanism.

In conclusion we can say that Eli Lilly got Prozac approved in Europe, even if different countries felt that the drug should not be approved for children. MHRA did not want to offend FDA (who approved Prozac for children in 2003) and wanted to save the only tool available for biological psychiatry (when all other antidepressants had been banned for children); the Agency wrote that "the profession" [psychiatry] *"must be able to prescribe something"*. The Swedish MPA wanted to approve Prozac so that good follow-up studies on the safety risks could be conducted *afterwards*.

As we have seen above, the follow-up studies came to nothing and the careful monitoring of children receiving Prozac (through different registers) did not happen. Eli Lilly got away with doing *nothing all*.

The only results of all follow-up requirements are that we, more than 20 years after Prozac was approved in the U.S. and 4 years after the drug was approved for children in Europe, can say that *new* rat studies have demonstrated a delay in sexual maturation, and that Eli Lilly conjured away the possible causal mechanisms in the new studies.

Can the medical agencies' betrayal of the children get much worse ?

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

[1] MPA, *Prozac / Prozac (fluoxetine) is approved for treating depression in children and adolescents,* 6 June 2006, http://www.lakemedelsverket.se/Alla-nyheter/NYHETER-2006/FontexProzac-fluoxetin-godkanns-for-behandling-av-depression-hos-barn-och-ungdomar/
[2] Today's Medicine, *Prozac may be used to treat depression in children,* 6 June 2006, http://www.dagensmedicin.se/nyheter/2006/06/06/fontex-far-anvandas-vid-dep/index.xml
[3] The Dutch Medicines Evaluation Board (CBG), *Prozac (fluoxetine) - Paediatric Indication, Rapporteurs' Assessment Report,* 31 October 2005, http://jannel.se/ProzacDutchAsessement31October2005.pdf
[4] The Dutch Medicines Evaluation Board (CBG), *Joint Assessment Report,* 6 February 2006, http://jannel.se/Prozac-JointAssessmentReport6February2006.pdf
[5] MPA, *Comments From The Medical Products Agency on the Final Variation Assessment Report (FVARS);* 29 April 2005 (Lena Björk, Hans Melander, Ulla Liminga, Eva Gil Berglund), http://jannel.se/Prozac-MPA-29April2005.pdf
[6] Eli Lilly, *Letter of Undertaking*, 31 May 2006. See Attachmen 5.1, http://jannel.se/Prozac-Lilly-RegulatoryResponsetoMHRA-sexual-maturation31Jan2007.pdf
[7] UK electronic Medicines Compendium (eMC), SPC Prozac, visited September 19, 2010, http://www.medicines.org.uk/EMC/medicine/504/SPC/Prozac+20mg+hard+capsules%2c+and+20mg+per+5ml+oral+liquid/
[8] Eli Lilly, *Draft Protocol, TADSjr*, September 29, 2006, http://jannel.se/Prozac.Lilly_DraftProtocol_TADSjr-sexmaturation29Sept2006.pdf
[9] Eli Lilly, *Response to Qs on TADS*, November 16, 2006, http://jannel.se/Prozac-Lilly-ResponseQs-TADSjr16nov2006.pdf
[10] MHRA, *Response Assessment Report*, December 12, 2006, http://jannel.se/Prozac-MHRA-ResponseToLillyon % 20SexualMaturation12Dec2006.pdf
[11] MHRA, *Revised Response Assessment Report*, December 19, 2006, http://jannel.se/Prozac-MHRA-ResponseToLillyon % 20SexualMaturationREV19Dec2006.pdf
[12] Eli Lilly, *Response to MHRA*, 31 January 2007; http://jannel.se/Prozac-Lilly-RegulatoryResponsetoMHRA-sexual-maturation31Jan2007.pdf
[13] MHRA, *Response Assessment Report 2*, 1 March 2007; http://jannel.se/Prozac-MHRA-assessment % 20of % 20responses2 - sexmaturation1March2007.pdf
[14] MHRA, *Request for Information*, 12 March 2007 http://jannel.se/Prozac-MHRA-RequestInformation12March2007.pdf
[15] Eli Lilly, *Response to MHRA*, April 12, 2007, http://jannel.se/Prozac-LillyRegulatoryResponeMHRA-12April2007.pdf
[16] MHRA, *Assessment Report*, April 23, 2007, http://jannel.se/Prozac-MHRA-AssessmentofResponses3-23April2007.pdf
[17] MHRA, *Request for Information*, 2 May 2007 http://jannel.se/Prozac-MHRA-ResquestForFurtherInformation-2May2007.pdf
[18] Eli Lilly, *Response to MHRA*, 21 May 2007, http://jannel.se/Prozac-Lilly-RegulatoryResponseMHRA21May2007.pdf
[19] Eli Lilly, *Revised Draft Protocol, TADSjr*, 6 July 2007; http://jannel.se/Prozac-LillyProtocolTADSjr-SexMat6July2007.pdf
[20] MHRA, *Final Assessment Report*, 19 July 2007; http://jannel.se/Prozac-MHRA-FINAL-AssessmentofResponses19July2007.pdf
[21] MHRA, *Assessment Report*, September 9, 2009, http://jannel.se/Prozac-MHRA.AssessmentReport9Sept2009.pdf
[22] MPA, *Dear Colleague,* September 21, 2009, http://jannel.se/Prozac-LV-FollowUp21Sept2009.pdf