

Antidepressants for Children

Prozac – how could it be approved for children in Europe?

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In December 2003, the British MHRA (Medicines and Healthcare products Regulatory Agency) banned the use of all antidepressants for children and adolescents under 18 years [1, 2]. There were no proven benefits with the drugs but evidence that they resulted in increased suicidal behaviour. The only antidepressants that MHRA specifically excluded from the ban was Prozac, earlier the same year approved by FDA [3, 4], based on two short studies (more about them later) .

On 25 April 2005 the European Medicines Agency, EMEA, published warnings for *all* antidepressants - *including Prozac*. They should not be given to children and adolescents diagnosed with depression [5], they increased the risk for suicidal behaviour and hostility. The British Medical Journal (BMJ) wrote: “The European Medicines Agency has ruled that selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) [newer classes of antidepressants] should not be prescribed for children and adolescents under the age of 18 [for depression]...” [6].

This created a very special situation. FDA had approved Prozac for children, the British MHRA had not wanted to offend FDA and leading psychiatrists and exempted Prozac from their ban of antidepressants, but now the EMEA issued warnings for *all* antidepressants – including Prozac – and “said ***“should not be given to children and adolescents “*** .

MHRA's angry reaction to the decision of EMEA told some of the pressure exerted on the agency. A spokeswoman for the agency said:

“There is still time to influence it [the decision]. We back what Emea’s scientific panel is saying but the key difference is that Prozac is the one drug for which there is clinical-trial evidence that it is effective. ***The profession know they are going to have to prescribe something*** and it is important they know what the dangers are and the best way of prescribing it. We think it is safe to use so long as it is monitored carefully.” [7] [Italics here.]

There was a strong pressure from the “profession” [psychiatry], which ***“have to prescribe something”***, and when it was not possible to prescribe Prozac, it became a big problem.

The directive from EMEA about Prozac to children went straight against the approval that FDA made in early 2003, in that a majority of experts from European agency now found that Prozac should not be given to children and adolescents.

And here is where this story starts. We did not know anything about the game behind the scenes – we did not know how it could be that the *same* authority – the European Medicines Agency, EMEA – one year later 6 June 2006 *approved* Prozac for children. The British Medical Journal then wrote: “The European Medicines Agency has approved the use of fluoxetine (Prozac) for children aged 8 years or more and teenagers who have moderate to severe depression...” [8]

How did the turnaround happen? What new information had emerged in one year? What forces pushed through the change of the decision?

None of this has been answered in the past for the simple reason that the records from the medical agencies telling the story have not seen the light.

To get an application approved of course first requires *an application*.

And a newspaper article from June 2004 [9] revealed: MHRA had in order to deal with the pressure *asked the pharmaceutical company Eli Lilly to submit an application for approval of Prozac in the UK and Europe*. A representative of a patient association, who quit the UK expert committee because of lack of transparency, was very upset that MHRA, who should oversee the pharmaceutical companies, contacted one of them and asked them to apply for an approval. He said: “This raises real issues about their impartiality. They are saying they want an SSRI [this type of antidepressants] to be given to children. It is not their job to decide such a thing. If they are going to do deals with the drug companies, where does it stop?”

Well, we already know that it stopped with Prozac being approved for children in Europe two years later. But it can already now be said that Sweden had at least as much to do with the approval decision being pushed through. UK and Sweden – and the psychiatric consultants that these countries made use of – pushed it through while several other countries strongly argued for *not* approving Prozac.

At the same time as EMEA (25 April 2005) issued warnings on all antidepressants and wrote “should not be used to treat depression in children and adolescents”, the Swedish Medical Products Agency, MPA, (29 April) submitted its comments to the evaluation done by France and UK about the application submitted by Lilly for the approval of Prozac (France *opposed* the approval). The Swedish Medical Products Agency (MPA) gave the following amazing assessment [10] (p. 1):

“...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].”

In other words, the Swedish MPA and the UK MHRA at this time supported the approval of Prozac for children.

The arguments for giving approval were strange, to say the least, they had little to do with any good scientific evidence that this was an effective and safe medicine for children. This is what the MPA had to say (p. 1):

“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.”

MHRA had used the absurd argument “the profession [psychiatry] know they are going to have to prescribe something”, and the reasons given by the MPA were of the same low class. The Swedish agency responsible for making sure that people got safe and effective medicines said they wanted to accept a psychiatric drug for children because doctors already prescribed it! The agency further stated that if Prozac is approved for children *now* they can *later* require further studies about the harmful effects.

With this logic one could easily approve *all* antidepressants to children – not to mention even more toxic psychiatric drugs, as psychiatrists already prescribe also these for children, despite all evidence of harmful effects.

Strangely enough the Swedish Medical Products Agency, eight days after EMEA issued directives about all antidepressants, convened its own expert meeting. Among the participants were the officials who signed the above assessment [10], as well as prominent consultants as Psychiatry Professor Anne-Liis von Knorring, scientific advisor to the Agency, and Psychiatry Professor Bruno Hägglöf. The result of this meeting was treatment recommendations for antidepressants for children – “an update of the state of knowledge” [11]. In those it was written that no antidepressants are approved for children, *but* that “it is well known that pharmacological treatment of children is sometimes deemed necessary and that antidepressants are used” (the same kind of argument that was used in the assessment above). About Prozac it is written: “Among antidepressant drugs fluoxetine has *the most convincing* clinical documentation ... ” [Italics here.] The risk of suicidal behaviour is mentioned, the risk that together with the absence of positive effect, got EMEA to eight days earlier, for *all* antidepressants announce: “*should not be given to children and adolescents*”. The experts in the MPA-meeting however go far to ignore the proven risk of increased suicidal behaviour (i.e. “not significant increase in risk compared to placebo”).

What is really strange is that the MPA *opposes* the just issued European warnings and that the Agency issues the positive statements about Prozac (“the most convincing clinical documentation”) when they know that several other medical agencies in Europe have another view on this. In addition, the MPA at this point knows that the investigation of Prozac is continuing at European level, that a variety of questions about the clinical trials of Prozac and the safety risks of the drug have been submitted to the manufacturer Eli Lilly, and that the answers from the company, when eventually received, will form the basis for a reassessment of the drug.

The continued handling of the case at European level was referred to Holland, who, in the role of “Rapporteur”, should request further answers from the pharmaceutical company Eli Lilly and submit a new evaluation.

On 31 October 2005 the evaluation from the Dutch Medicines Evaluation Board (CBG) was issued: *Prozac (fluoxetine) - Paediatric Indication, Rapporteurs' Assessment Report.*[12]

It is an incredible report. It begins with the words:

“It is not recommended to grant an indication to fluoxetine for the treatment of depression in children and adolescents because the benefit/risk balance in the claimed indication is deemed negative.”

In other words, Prozac should *not* be approved for depressed children and adolescents; the dangers of the drug are greater than any benefit.

Note that *this* evaluation is made about 10 years after the prescription of Prozac for children in the United States began to rise heavily (although the drug was not approved for children), and nearly three years after FDA (January 2003) approved Prozac for children. Please note that the evaluation is made *after* the Dutch Medicines Evaluation Board asked for and received answers to a number of follow-up questions from the company Eli Lilly.

The “unresolved issues” around Prozac, the reasons why different medical agencies in Europe in the end of April 2005 rejected Lilly's application for approval was taken up by the Dutch medical agency:

“Overall there were unresolved objections and concerns with respect to the following issues:

Efficacy:

- Representativeness of the included patient population.
- The lack of information regarding optimal dose.
- The limited information regarding long-term efficacy.

Safety from clinical studies:

- Higher rates of suicidal related events in the fluoxetine compared to placebo treated patients.
- Concerns about reduced height and weight gain.
- Lack of data concerning effects on maturation, cognition and behavioural development.
- Limited long-term safety data.

Preclinical safety:

- Effects on bone development.
- Effects on sexual development.
- Irreversible testicular toxicity.
- Effects on emotional development.”

It was these questions and others that the Dutch Medicines Evaluation Board (as “Rapporteur”) should give further consideration and on which the agency requested additional information from Eli Lilly.

So what was the reason that the “Rapporteur” in October 2005, *after having received the replies from Eli Lilly*, stated that Prozac could *not* get an approval in Europe?

The Board referred to what was already known and said that the answers from Lilly had not diminished worries of damage. They wrote:

“Concerns about safety issues were not resolved, specifically concerns about suicide related behaviours, including suicide attempt and suicidal ideation, and, from non-clinical data, about the effect on growth, sexual maturation, cognitive and emotional development. The limited evidence concerning long-term safety is a concern as well, especially given these safety signals.”

The Board further questioned whether the descriptions of positive effects in the studies submitted had anything to do with the actual effect in clinical activities (more about that later):

“Moderate effects, though somewhat inconsistent across trials, were seen, but there are doubts about the external validity of these results due to the stringent selection procedure.”

The Board further wrote:

“In addition to objections that were raised in response to the request, during the course of this procedure new information concerning safety have become available from preclinical as well as clinical studies. Animal studies have raised concerns with respect to effects of early exposure on growth and sexual maturation. A non-company sponsored clinical study (the Treatment of Adolescents with Depression Study (TADS)) demonstrated that fluoxetine, in common with other SSRIs, is associated with increased risk of suicidal behaviours in young persons.”

Comments about the “efficiency” of Prozac

In the report the Dutch agency then assesses the clinical trials that were part of the application, which should show that Prozac was “effective” for children and adolescents, one of the requirements for the approval of the drug.

The Board writes (p. 9) that the evidence of efficiency is “mixed – a modest effect that reached significance only in some trials...”. But, as they write, “more important is the fact that the patients population that was included in the trials is a highly selected group that is not likely to be representative of the total depressed patient population”.

The Board explains in detail how the various studies of Prozac were done, and compare them with other studies of antidepressants in children. It is explained that Eli Lilly and the researchers who conducted the trials of Prozac had used another method than what had been used in the trials of other antidepressants. For example, all children who would participate in the Prozac studies, had to undergo “an extensive screening and evaluation procedure” *before* they became included in the actual studies, with the result that many were excluded from the studies. Part of this extensive procedure was (in two of the studies) that all children before the actual study were given a placebo (sugar pill) for a week. The children who showed improvement when they received placebo were excluded from the study. We know from other

trials of antidepressants that *a high proportion* of those receiving placebo improved just as much as those receiving antidepressants. In other words, when comparing the groups one gets no positive effect of the antidepressant drug, compared to placebo, which in itself shows that the drug does not work, it does not have a positive chemical effect (placebo works just as well).

So the reason they gave all children placebo for a week before they began the actual study was to be able to exclude children who got better on placebo, and thus it was expected that a smaller proportion of children who received placebo *in the actual study* would get a positive result. The researchers wanted to increase the chance of obtaining a difference between the active drug (Prozac) and placebo, increasing the chance of obtaining “evidence” that Prozac was “effective”.

It was this approach that the Medicines Evaluation Board was referring to when they wrote about “a highly selected group”. The Board also made the comparison to what happened when researchers in *other* studies of antidepressants did *not* from the beginning exclude children that could worsen the results of the drug versus placebo. A comparison is made with the studies of paroxetine (Seroxat/Paxil) where a “lower percentage of patients were excluded”. The Board said: “Comparison of the results indicate that the percent responders in the active arms are similar in the paroxetine and the fluoxetine trials ... *while the percent responders to placebo are generally higher in the paroxetine trials.*” [Emphasis added.] In studies with paroxetine, the proportion of “placebo responders” was 55%, 58%, 46%, whereas in studies with fluoxetine it was 32%, 53%, 35%. Exclusion of children in the Prozac studies *strongly diminished the proportion who received a positive result on placebo* – thus creating a “positive” difference between the antidepressant and placebo; with this approach Eli Lilly could argue that Prozac was “effective” – which the Dutch Medicines Evaluation Board did not agree to.

Conclusions on the “safety” of Prozac

The Dutch Medicines Evaluation Board summarizes the safety risks :

“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.”

They note again that Prozac can not be approved (the benefit is not greater than the risk) and write:

“The company should be encouraged to conduct further trials, concerning the dose, the efficacy in a more general population and concerning long-term safety.”

And so Prozac got approved

The above means that in the end of 2005, the medical agency in Europe that had been responsible (as “Rappporteur”) to investigate the matter, considered that Prozac was *not* acceptable for children. It had raised a number of issues for the pharmaceutical company, but found that the answers the company provided did *not* change anything in the assessment. Prozac was not approved.

In the additional documents in the case it can be seen in the summary report from 6 February 2006 (Joint Assessment Report) [13] that several countries (France, Ireland and Denmark) supported Holland's assessment that Prozac cannot be approved for children and adolescents. The updated assessments from the “Rappporteur”, the Dutch medical agency, shows that at crucial points it is written ”Issue not resolved”, while estimates from the Swedish Medical Products Agency (“Co-Rappporteur”) of these points are ”Issue solved” or ”Issue to be discussed with the company ”.

The Dutch agency expresses its deep disappointment with the pharmaceutical company Eli Lilly and writes (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 Board also states:

“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.”

And based on this information the European Medicines Agency (EMA) the 25-27 April 2006, is conducting hearings in London with Eli Lilly. Now they agree, and now it goes fast. On 6 June, an approval is granted for Prozac! It is associated with ”requirements” for a number of follow-up studies – on the very safety issues that should have been resolved before an approval was granted.

The Swedish Medical Products Agency tells on its website [14]: “Fontex/Prozac (fluoxetine) is approved for treating depression in children and adolescents ”, and says that ”EMA decided to recommend that Prozac is approved for treating depression in children and adolescents over eight years of age”. It further says: “The Scientific Committee, the CHMP [Committee for Human Medicinal Products, experts in EMA from the various countries], states that studies in children and adolescents demonstrated that fluoxetine is effective against moderately severe and severe depression.”

The MPA of course says nothing about the story above. There is nothing in the MPA statement about the previously used “scientific arguments” that ”*The profession know they are going to have to prescribe something...*” (MHRA) [7] and that Prozac should be approved because it is already used for children [MPA] [10].

In its assessment from April 2005 [10] the MPA also told that one of the good grounds on which it would approve Prozac for children was that one *then* – after the approval – got good chances for “better post marketing surveillance in these populations and possibilities to request further studies”.

What happened with this may require a separate article. The wise reader can 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 MHRA, MPA and Eli Lilly after the approval start with new effective follow-up actions for the children who received Prozac?

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Here you can read the full report from Holland: CBG, The Dutch Medical Evaluation Board, Prozac (fluoxetine) - Paediatric Indication, Rapporteurs' Assessment Report, 31 October 2005, <http://jannel.se/Prozac-HollandAR.pdf>

- [1] The Independent, *Threat of suicide leads to ban of major antidepressants for children*, 10 December 2003, <http://www.independent.co.uk/life-style/health-and-families/health-news/threat-of-suicide-leads-to-ban-of-major-antidepressants-for-children-576211.HTML>
- [2] Medical News Today, UK - *Major antidepressants banned - Suicide Threat*, 13 December 2003, <http://www.medicalnewstoday.com/articles/4861.php>
- [3] M2 Press Wire, *FDA Approve Prozac for Pediatric use*, 6 January 2003, <http://www.encyclopedia.com/doc/1G1-96148926.html>
- [4] FDA, *Approval of Prozac for Pediatric Use*, FDA Patient Safety News, 14 April 2003, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=14>
- [5] EMEA press release, *The European Medicines Agency finalis review of antidepressants in children and adolescents*, 25 April 2005 <http://www.ema.europa.eu/pdfs/human/press/pr/12891805en.pdf>
- [6] BMJ, *Regulator restricts use of SSRIs in children*, 30 April 2005, <http://www.bmj.com/cgi/content/extract/330/7498/984-a>
- [7] The Independent, *Britain set for clash with Europe over ban on Prozac for under - 18s*, 26 April 2005, <http://www.independent.co.uk/life-style/health-and-families/health-news/britain-set-for-clash-with-europe-over-ban-on-prozac-for-under18s-522211.html>
- [8] BMJ, *European agency approves use of fluoxetine for children and teens*, 17 June 2006, <http://www.bmj.com/cgi/content/extract/332/7555/1407-a>
- [9] The Guardian, *Safety alert on adult use of antidepressants*, 14 June 2004, <http://www.guardian.co.uk/news/2004/jun/14/uknews>
- [10] MPA, *Comments From The Medical Products Agency, On The Final Variation Assessment Reports (FVARS)*; 29 April 2005, (Lena Björk, Hans Melander, Ulla Liminga, Eva Gil Berglund) .
- [11] MPA, *Pharmacological treatment of depression in children and adolescents - an update of the state of knowledge - Treatment Recommendation*, May 2005 ; http://www.lakemedelsverket.se/upload/health-medical_care/reading/depressionbarn.pdf
- [12] CBG, The Dutch Medical Evaluation Board, *Prozac (fluoxetine) - Paediatric Indication, Rapporteurs' Assessment Report, 31 October 2005*, <http://jannel.se/Prozac-HollandAR.pdf>
- [13] CBG, The Dutch Medical Evaluation Board, *Joint Assessment Report*, 6 February 2006.
- [14] MPA, [Swedish] *Fontex/Prozac (fluoxetin) godkänns för behandling av depression hos barn och ungdomar*, 6 June 2006, <http://www.lakemedelsverket.se/Alla-nyheter/NYHETER-2006/FontexProzac-fluoxetin-godkanns-for-behandling-av-depression-hos-barn-och-ungdomar/>