Prozac for young persons—what happened with the follow-up studies and the "increased risk for suicide related behaviours"?

January 17, 2015

Prozac (fluoxetine) 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 claimed it was a good idea to ***first*** approve Prozac and ***afterwards*** do the needed safety studies.

The UK medical agency MHRA was the Reference Member State (RMS), leading the investigation, and the Dutch drug regulatory agency (CBG) was responsible for handling the assessment of the matter together with the Swedish Medical Products Agency (MPA).

The Dutch CBG ("Rapporteur"), was against the approval of Prozac for children and wrote in October 2005:

> **"It is <u>not recommended</u> 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." [3]**

The Dutch CBG summarized 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."**

The agency noted again that Prozac cannot be approved (the benefit is not greater than the risk) and wrote:

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

But in June 2006 Prozac was approved for children anyway—without any further studies.

The sordid details about how that was done, with all relevant documents, can be read here
Prozac - how could it be approved for children in Europe?
http://jannel.se/prozac.childrenEU.pdf [4],
Prozac for children —what happened with the follow-up?
http://jannel.se/prozac-children-partII.pdf [5] (some links no longer working).

We could see in the documents that the Swedish Medical Agency, 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]**

We could from the documents **[4]** in 2010 see that the follow-up studies came to nothing and that the careful monitoring of children receiving Prozac (through different registers) did not happen. Eli Lilly got away with doing *nothing all*.

We could see that 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 profession" [psychiatry] *"must be able to prescribe something".* We could see the arguments from the Swedish MPA, that Prozac was already prescribed to children and that it thus was better to get in control of this by approving the drug (!), so that good follow-up studies on the safety risks could be conducted *afterwards,* together with "better post marketing surveillance",

And we come to what this updated article is all about, **"the better post marketing surveillance** [in Sweden] **in these populations"**, that was to be the effect of the approval of Prozac in 2006.

As the warnings about *increased suicidality risk* with antidepressants was extended to young adults (18-24) in May 2007 **[7]**, we extend the investigation about these follow-up actions to this age group. As the absolute most frequent prescriptions of Prozac (and other antidepressants) in Sweden have been for women **[8]**, the investigation is limited to the group of young women 15-24 (6% of all young women got antidepressants 2013).

What is left of the **"better post marketing surveillance",** after the follow-up studies (that came to nothing) are counted out, are the adverse event reports submitted to the Medical Products Agency (MPA) in Sweden, and their analysis and follow-up.

What do we find about adverse event reports from treatment with Prozac resulting in suicide among young women 15-24 in the years 2006-2013?

We find: There are *no* adverse event reports about Prozac treatment resulting in suicide during these eight years—*not one single report*.

But as we cannot limit the investigation to only Prozac —all SSRI antidepressants (Prozac, Zoloft, Seroxat/Paxil, Cipramil) and other newer antidepressants (Effexor, Cymbalta, Cipralex) have essentially the same effect and the same warnings about suicidality—we must also look for the adverse event reports about suicides, submitted for all other antidepressant drugs.

We find: There is *one* adverse event report about an antidepressant drug (Cymbalta) treatment resulting in suicide during these eight years—*one single report*.

This means that the Swedish MPA in its yearly reports can say "no new safety signals have been detected"; the involved pharmaceutical companies can, in their "Periodic Safety Update Reports", tell that NO adverse event report [except one] about suicide have been reported in connection with antidepressant treatment for eight years; the ongoing campaign, from the same companies and their affiliated psychiatrists and statisticians, to make nothing of the warnings issued can continue to succeed; the uncritical media can tell that antidepressants seem to "normalise a chemical imbalance" and "protect" against suicide.

Were it not for two crucial circumstances:

a) That almost all suicides in Sweden are subjected to forensic investigations, in which toxicological analyses are done to find traces of psychotropic drugs, other medicines, alcohol and illegal drugs.

b) The good Swedish Freedom of Information Act, making it possible to get access to these data in a deidentified form.

What do we find about Prozac and other antidepressants in these analyses of suicides of young women in the eight years 2006-2013?

We find that 30 of the 293 cases examined (92% of all suicides among these women) had Prozac in their blood at the time of the suicide, meaning that 10% of these young women were treated with and took Prozac up to the time of their death. And remember, *none* of these treatments, ending in death, were reported to the Medical Products Agency as a serious adverse event.

We find that *106 of the 293 young women—38%—had antidepressants in their blood at the time of death. One* of these treatments, ending in death, was reported to the Medical Products Agency as a serious adverse event.

We find:

- Prozac (fluoxetine) in 30 cases;
- Zoloft (sertraline) in 24 cases;
- Cipramil (citalopram) in 23 cases;
- Effexor (venlafaxine) in 23 cases;
- Mirtazapine in 9 cases;
- Cymbalta (duloxetine) in 5 cases;
- Clomipramine in 3 case;
- Amitriptyline in 2 cases;
- Paroxetine and reboxetine in 1 case each.

Altogether 121 cases (meaning that 15 young women took more than one antidepressant at the time of death); in addition to all other psychiatric drugs found in the analyses.

This is what the "post marketing surveillance" in Sweden shows for Prozac and other antidepressants for young women, in the years 2006-2013:

106 of the 293 young women who committed suicide—38%—had antidepressants in their blood at the time of the suicide.

1 of these cases was reported to the Medical Products Agency in form of an adverse event report.

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[1] Today's Medicine, *Prozac may be used to treat depression in children,* 6 June 2006, http://www.news-medical.net/news/2006/06/08/18359.aspx
[2] MPA, *Prozac/Fontex (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/
[3] CBG, The Dutch Medical Evaluation Board*, Prozac (fluoxetine) - Paediatric Indication, Rapporteurs' Assessment Report*, 31 October 2005, http://jannel.se/Prozac-HollandAR.pdf
[4] Janne Larsson, *Prozac - how could it be approved for children in Europe?* 22 July 2010, http://jannel.se/prozac.childrenEU.pdf (some links no longer working)
[5] Janne Larsson, *Prozac for children —what happened with the follow-up?* 21 September 2010, http://jannel.se/prozac-children-partII.pdf (some links no longer working).
[6] 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
[7] FDA, *The FDA Proposes New Warnings About Suicidal Thinking, Behavior in Young Adults Who Take Antidepressant Medications,* May 2, 2007
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108905.htm
[8] The National Board of Health and Welfare, The Register on Prescribed pharmaceuticals in Sweden, http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel