

## Paxil Study 329 All Over Again?

Something has been bugging me about the [Paxil NCT00812812 trial](#) currently being run by GlaxoSmithKline in Japan. Enough to keep me awake at night to ponder the 112487 trial Protocol and its content, in particular, the exclusion criteria.

For those of you who don't know, the Paxil NCT00812812 trial, underway at this moment in time, is for children from the age of 7 upwards to 17 - Yes, you read it correct, CHILDREN!

It's hard to fathom out why GSK would be yet again trying to target children with a drug that, by their own admission, is NOT safe in this particular age group. One can only assume that GSK believe the genetic make-up of Japanese subjects is significantly different to those of the Western population, unless of course they have other reasons for wanting to gain a license for use of Paxil in children?

Just because this is Japan does not mean that we should ignore what GSK's intentions are here. They wish for children to take a drug that is dangerous and harmful - it's safe to assume that isn't it?

The criteria for inclusion into this trial stipulates that the subjects must be between the ages of 7 to 17 - in other words, Children. It also stipulates that the subjects must have Major Depressive Disorder [MDD]. They measure the level of depression according to the DSM-IV-TR criteria - Depressive disorders: MDD, single episode (296.2), MDD, recurrent (296.3). To the layman, this means children who have major depression.

The exclusion list for this trial is lengthy to say the least and it would appear that GSK want the 'best' of a 'bad' bunch.

### Exclusion Criteria

run-in period: A subject will not be eligible for inclusion to this study if any of the following criteria applies at start of run-in period:

Patients who in the investigator's judgment presented with a clinically predominant Axis I disorder other than MDD (e.g. dysthymic disorder, eating disorders, Specific phobia, PTSD, OCD, Panic disorder, etc)

Patients with any history of a psychotic episode or psychotic disorder (including schizophrenia )or complication of these diseases.

Patients with a history of a bipolar disorder, or complication of these diseases.

Patients with Attention-Deficit, or Hyperactivity Disorder

Patients with Mental Retardation or Pervasive Development Disorder

Patients diagnosed with Substance Abuse or Dependence within 12 weeks prior to the Screening visit

Patients with past treatment experience with the investigational drug (i.e. paroxetine)

Patients treated with electroconvulsive therapy in the immediate 12 weeks prior to the Screening visit

Patients with past history of serotonin syndrome and neuroleptic malignant syndrome.

Patients with CDRS-R score of "suicidal ideation" of 3 or greater. Or patients whose C-SSRS assessment suggests that they are or have been at significant risk for harming themselves or have actually harmed themselves, or who, in the opinion of the chief investigator (subinvestigator), are at significant risk for harming self.

Patients with past history of suicide attempt, self harm(excluding "no suicidal intent " ), or an intentional overdose (excluding obviously unintentional overdose)

Patients who have been treated with other clinical trial investigational drug (including post-marketing clinical trial) in the immediate past 3 months of the Week -2 visit.

Patients who have taken antidepressant medication 1 week prior to screening.

Patients with complicated disease of glaucoma.

Patients with convulsive disorders such as epilepsy or past history of these diseases.

Patients regularly using drugs (e.g. NSAIDs) that would increase the risk of hemorrhage, or patients with bleeding tendency or hemorrhagic diathesis.

Patients with severe renal and hepatic disorder.

Patients with serious organic disorder in the brain.

Patients with chronic hepatitis type B and/or C which is positive of hepatitis B surface antigen (HBsAg) and/or hepatitis C antibody.

Patients with a current history of carcinoma or malignant tumor, or complication of these diseases.

Female patients who are pregnant, lactating, or who might be pregnant, or who wish to be pregnant during the study period

Patients in the opinion of the chief investigator (subinvestigator) judged as not eligible for the study.

Patients with clinically significant comorbid impulsivity symptoms. (e.g. Personality Disorder, Conduct Disorder)

treatment period: Subjects for whom any of the following categories apply at Week 0 (start of the treatment period) will not be progressed to the treatment phase.

Patients with CDRS-R score of "suicidal ideation" of 3 or greater, or patients who, in the opinion of the chief investigator (sub investigator), are at significant risk for harming self

Patients with variation of the CDRS-R total raw summary score at Week 0 of +/-25% or greater compared to that of Week -2.

Patients with drug compliance of Drug 1 (run-in placebo) from Week -2 to Week 0 less than 80%.

Patients, in the opinion of the chief investigator (sub investigator) judged as not appropriate for the study.

Quite a list, I'm sure you would agree?

Forget the scientific talk, it's aimed to confuse. What one has to do here is read between the lines to see exactly what GlaxoSmithKline want from this trial.

The last exclusion listed is quite open-ended wouldn't you agree?

Why list such a vague exclusion after naming all other exclusions?

*"Patients, in the opinion of the chief investigator (sub investigator) judged as not appropriate for the study."*

This could mean anything and could possibly mean that any subject that could be detrimental into getting Paxil a license will be removed from the trial. That's my train of thought anyway. Am I right to question the motive behind this vague statement? One only has to study the

Paxil 329 study to see how GSK massaged data to gain a license for children all those years ago. A license that was obtained by fraudulently manipulating figures - something GSK have never been held accountable for... unless a slap on the wrists counts as a punishment?

Does the whole world need to be reminded of the infamous SmithKline Beecham

Paxil 329 study again?

Are they trying to gain a license for Paxil in children in Japan because of the language barrier?

CYP450-2D6 is a phrase some of you may not have heard of before and, I believe, it's one that GSK don't want you to hear about either.

To cut a long story short, anyone who is deficient in the CYP450-2D6 Cytochrome can be at danger if they take Paxil. There is no easier way to say it folks.

This, I believe, bothers GSK with regard to Paxil, so much so that it was announced in March 2006 that GSK had 'solved' the Structure of Human Cytochrome P450 2D6 [1]

The 2D6 deficiency differs from culture to culture. In Asia approx 60% of the Asian population (Thai, Chinese & Japanese) are poorer than normal metabolizers of drugs such as Paxil, which primarily use the 2D6 enzyme.[2] Which begs the question if the final exclusion, [*"Patients, in the opinion of the chief investigator (sub investigator) judged as not appropriate for the study."*] - actually means this population of 60%?

If GSK are going to pre-screen for this deficiency then any positive outcome of the trial will be cleverly disguised as an out and out success - 'The 'best' of a 'bad' bunch remember? Unless of course GSK step up to the plate and state clearly that 2D6 deficient subjects were removed from the trial?

So in essence, GSK want a bunch of kids with MDD. They don't want these kids to have any of the illnesses, traits, habits included on their exclusion list - anything that may cause a negative finding during the trial.

So, let's predict that the Paxil NCT00812812 trial is a success for GSK. They are granted a license for Paxil, moreover for use of Paxil in Japanese children. How many children will then

be prescribed Paxil by GP's, healthcare professionals who will use the same criteria as GSK did for the trial?

Take a look at the exclusion criteria again. Imagine if you will the scenario of a distraught

mother with her 16 year old son. She has gone to see her Japanese doctor because her son is showing signs of major depressive disorder. The exclusions for this trial need to be changed into questions for doctors to ask patients before they prescribe them Paxil. In this scenario, do you think the doctor would ask the mother of

this child the following questions:

Is your son 2D6 deficient?

Does your son have predominant Axis I disorder other than MDD (e.g. dysthymic disorder, eating disorders, Specific phobia, PTSD, OCD, Panic disorder, etc)?

Has your son ever had any history of a psychotic episode or psychotic disorder (including schizophrenia ), or complication of these diseases?

Does your son have a history of a bipolar disorder, or complication of these diseases?

Does he have Attention-Deficit, or Hyperactivity Disorder?

Does he have Mental Retardation or Pervasive Development Disorder?

Has your son ever taken any drugs that have led to Substance Abuse or Dependence?

Has he ever been treated with Paxil before?

Has he, in the past 12 weeks been treated with electroconvulsive therapy?

Does he have a past history of serotonin syndrome and neuroleptic malignant syndrome?

Does he have a CDRS-R score of "suicidal ideation" of 3 or greater. Or did his C-SSRS assessment suggest that they he has been a significant risk for harming himself or has actually harmed himself?

Does he have a past history of suicide attempt, self harm(excluding "no suicidal intent " ), or an intentional overdose (excluding obviously unintentional overdose)?

Does he have glaucoma?

Does he have convulsive disorders such as epilepsy or past history of these diseases?

Is he using drugs (e.g. NSAIDs) that would increase the risk of hemorrhage, or has he had bleeding tendency or hemorrhagic diathesis?

Does he have severe renal and hepatic disorder?

Does he have a serious organic disorder in the brain?

Does he have chronic hepatitis type B and/or C which is positive of hepatitis B surface antigen (HBsAg) and/or hepatitis C antibody?

Does he have a current history of carcinoma or malignant tumor, or complication of these diseases?

Does he have clinical significant co morbid impulsivity symptoms. (e.g. Personality Disorder, Conduct Disorder)?

Finally, one question the doctor WILL NOT be able to ask this mother would be  
Has he, in the opinion of a 'specialist', been judged as not appropriate for Paxil?

A huge list of questions for any doctor but ones that should be asked if Paxil is granted a license for use in children in Japan. If it's good enough for GlaxoSmithKline to exclude subjects from the trial because they don't meet the criteria then it's fair to say that doctors should be concerned and ask the patient or the patient's parents the above questions.

Two questions I have put to GlaxoSmithKline in an email are thus:

1- What exactly does the exclusion criterion "Patients in the opinion of the chief investigator (subinvestigator) judged as not eligible for the study" mean? What other criteria might this include not already listed. Could it possibly mean that children & adolescents will be pre-screened, by genetic testing to be sure that they are not deficient in the CYP450-2D6 enzyme that Paxil desperately needs to be safely cleared from a persons system. Will these kids not be included in the study?

2- Does the long list of exclusion criteria really represent the real world of kids that will be prescribed this drug in Japan, if it is approved. Will doctors use this same list of criteria when deciding to prescribe Paxil to their young Japanese patients?

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You have to ask yourselves if GlaxoSmithKline used the same criteria in other trials for Paxil other than trials for children. Whatever or whomever they excluded in all of the Paxil trials should be made abundantly clear to doctors before any prescription is ever written for Paxil - that's fair game isn't it?

Paxil has been proven to be as useful in children as a one-legged man at an arse kicking contest and as dangerous as giving them a loaded gun. I predict the results of this current trial will be favourable to GlaxoSmithKline. I also predict that doctors will not be made aware of reasons NOT to give Paxil to children [Exclusions]

To put it bluntly and to use an analogy:

Here we have a rollercoaster in an amusement park, a rollercoaster that was condemned because it was faulty. The greedy amusement park owner wishes to re-open the rollercoaster, despite knowing how dangerous it is - so he has trial runs to prove to the public that children with ginger hair will be safe. Absurd isn't it - and nobody in their right mind would deem this acceptable behaviour. Yet here we have GlaxoSmithKline, the faultless pharmaceutical

company who are deluded enough to believe that they have never done any wrong where Seroxat/Paxil is concerned. They are re-launching the rollercoaster... but first they need a license and they will do everything in their power to gain that license.

I hope I'm wrong.

Bob Fiddaman

<http://fiddaman.blogspot.com>

[1]-<http://www.analytica-world.com/news/e/53265/>  
[2] Bernard et al, J Pharm Sci 96-2007

#### RELATED STORIES

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Glaxo - Turning Japanese!

Email to Japanese Embassy regarding New GSK paroxetine study in Children. ClinicalTrials.gov Identifier: NCT00812812

GSK Just won't stop trying to push paroxetine on children!

Email to Ministry of Health - Japan

[Japan Says Suicidal Cases Rise Among Paxil Users](#)