DAVID HEALY – JULY 30TH
APPENDIX 3 A:
ZOLOFT HEALTHY VOLUNTEER STUDIES

The issue of the suicidal and homicidal effects of Zoloft get tied up with the illnesses they are used to treat. These healthy volunteer studies help to show that completely normal people can become suicidal and violent when exposed to treatment, and more to the point can be legally insane – Zoloft can make them act in ways that are out of character.

Pfizer's Healthy Volunteer Studies

It is standard practice for a company to run a number of the healthy Volunteer studies prior to clinical testing. These are sometimes called phase 1 studies and are mostly designed to look at aspects of safety on treatment.

The majority of Zoloft studies were done for pharmacokinetic and pharmacodynamic reasons and many of these were single dose studies. They were not designed to pick out the distinctive functional effects of Sertraline – either beneficial or adverse. Many of these studies had very high rates of sexual dysfunction or extrapyramidal reactions reported, while others have almost no sexual dysfunction reported. This points to the insensitivity of the testing system.

For a variety of reasons, the studies with the highest reporting rates are more likely to be offering the correct rate of occurrence of these problems.

There do not appear to have been any tolerance studies exclusively dedicated to establishing the psychotropic effects of the new compound. This is disturbing as Zoloft contained a new pharmacological principle, the functional or behavioral effects of which were not well known in the 1980s when these studies were carried out. In my opinion the failure to carry out more specific studies constitutes a disservice to both the scientific and the clinical communities. But reports on Pfizer's healthy volunteer studies reveal company personnel were aware of the findings from other studies being carried out in healthy volunteer studies with other SSRIs and incorporated these findings into their assessments of what studies with Zoloft revealed.

The material reported here has been selected to make the point that a drug like Zoloft can affect anyone and also to avoid breaching prior confidentiality orders. The focus is primarily on Study 206 and a healthy volunteer study done in my laboratory. If the Court needs a more comprehensive overview of the Zoloft healthy volunteer studies I will be happy to provide it.

In brief, Pfizer's multiple dose tolerance studies show high dropout rates – up to 50% in one study and approx 13% otherwise. From studies where the design permits an assessment, withdrawal syndromes indicates that roughly 50% of participants had withdrawal issues. Mood change appears to occur at a 25% rate with agitation occurring at a 33% rate and sexual dysfunction where recorded at approximately 40%. Extrapyramidal features such as tremor, and mouth/throat dyskinesias or dystonias occur in roughly 30%.

There is a broad consistency between the findings seen in Zoloft studies and findings from SmithKline Beecham's single or repeated dose studies in healthy volunteers with Paxil, which show a similar adverse event profile, with studies being abandoned after a single dose and volunteer drop-outs after a single dose. The profile of side effects appears similar to that in the multiple dose studies – nausea, insomnia, lethargy or malaise and a range of extrapyramidal symptoms such as agitation.

These side effect profiles overlap with that found in the healthy volunteer study conducted in our laboratory using Zoloft, in which there were rates of sexual dysfunction of approximately 40% reported and extrapyramidal changes involved dystonias and dyskinesias of the throat and jaw area in up to 50% of cases and rates of akathisia or agitation of approximately 25%. They are also consistent with data from other healthy volunteer studies utilising paroxetine that I have had the chance to review. And they are consistent with the clinical literature on sertraline and other SSRIs.

Protocol 206.

This was a double-blind placebo controlled study of Zoloft 150mg, in 12 female volunteers ages 34 – 40.

An internal company report by Doogan and Foulkes on Protocol 206 stated that:

"The study … terminated on 13th March 1983 (Day 4) after complaints by the volunteers that they were experiencing intolerable side effects.. these side effects were all volunteered independently, without communication between volunteers… since there was a clear cut difference in side effect reporting between placebo and sertraline and as the volunteers were experiencing marked discomfort the study was terminated".

"All sertraline subjects reported side effects from the first day of dosing. The severity and number of the side effects were such that by the 4th day of treatment only 1 out of 5 sertraline subjects was taking the medication".

"The degree of adverse reaction reporting necessitated premature termination of this study. All of the sertraline subjects but only one placebo subject experienced marked intolerance to the study drug. The nature of the side effects (apprehension, insomnia, hyperkinesias and tremors) suggest that sertraline was exerting stimulating effects.

The majority of side effects have been reported previously with subjects receiving other 5HT reuptake inhibitors, e.g. zimelidine, fluvoxamine and citalopram.

Therefore it is likely that these side effects are due to 5HT reuptake inhibition".

In appendix 11 is displayed... the most common side effects [which] were insomnia, headache, nausea/vomiting, agitation/anxiety, tremor, muscle spasms. .. Only for insomnia, agitation/anxiety, tremor and muscle spasms is there an indication of a dose relationship.

The material below is taken from diaries kept by the subjects taking Zoloft.

Subject 1
Day 1 Moderate insomnia and dizziness
Severe nausea and coldness.
Plus restless, faint, blurring, weak, tremor

Day 2 Moderate insomnia and dizziness
Severe nausea and coldness.
Plus restless, faint, blurring, weak, tremor
Discontinued

Day 3 Severe headache, nausea and coldness

Plus restless, apprehension, faint, dizzy, blurred, weak, tremor.

Day 4 Moderate nausea and coldness.
Plus faint, dizzy and weak

Day 5 Mild nausea

Subject 3
Day 1 Nil

Day 2 Mild insomnia, restlessness, headache, nausea, weakness, tremor

Day 3 Severe insomnia, restlessness, headache,

Day 4 Severe insomnia, moderate restlessness and headache.

Day 5 Feel wide awake, jaw and swallowing problems.- above there but mild

Subject 5
Day 1 Severe drowsy, insomnia, restlessness, nausea and tremor
Moderate apprehension, faint, palpitations, sweating, weakness plus shivering

Day 2 Severe drowsy, insomnia, restlessness
Moderate apprehension, faint, palpitations, sweating, weakness plus shivering

Day 3 Severe insomnia and restlessness
Moderate drowsy, apprehension, palpitations, sweating
Discontinued

Day 4 Severe drowsy, insomnia, restlessness, nausea and tremor
"now I've begun to write, I notice my hands are not steady"

Day 5 Severe insomnia and restlessness

Subject 6
This subject was supposed to be taking placebo but had detectable sertraline in their blood, making the occurrence of these side effects even more dramatic.

Day 1 Moderate headache and nausea

Day 2 Moderate headache and nausea
Plus tremor, lack of co-ordination.

Day 3 Severe insomnia,
Plus aggression and tiredness and restlessness
"felt aggressive in relationships and while driving"
Discontinued

Day 4 Moderate drowsy.

Subject 10

Day 1 Severe drowsy, insomnia, nausea
Moderate faint, dizzy, plus mild tremor
"rather fuzzy headed and disoriented"

Day 2 Severe insomnia and apprehension
Moderate drowsy, faint, dizzy, blurred, sweating,

Day 3 Severe apprehension and palpitations
Swallowing a problem and coldness,
Moderate tremor, headache, dizzy, faint, sweating,

"Its as though I'm suffering from anti-depressant poisoning – cold clammy skin, with waves of heat flushing through me – a feeling of terrible faintness – had to go to bed and swallow ? of milk – took about two hours to feel a bit better. Phone call from ? – discontinue the pills if we wished – side effects rather excessive".

Day 4 "Still feeling very shaky.. my head feels less muddled. My jaw seems to be clenched all the time and my back teeth ache. The capsules didn't work or seem to work until the afternoon and then the side effects were quite excessive."

Day 5 "Still.. a general feeling of being unwell".

Subject 12

Day 1 Severe drowsy, insomnia, restless, apprehensive, faint, weak, tremor.
Moderate dizzy

Day 2 Severe drowsy, insomnia, restless, apprehensive, faint, weak, tremor.
Severe swimming
Moderate dizzy
"The general feeling was like having the flu"
Discontinued.

Day 3 "my jaws were very tense, I felt if I opened my mouth my jaw would snap.

Protocol 207 – 1983

Published in 1986 as Saletu B Grunberger J, Linzmayer L (1986)
On the central effects of serotonin reuptake inhibitors: quantitative EEG and psychometric studies with sertraline and imipramine. J Neural Transmiss 67, 241-266.

5 males, 5 females, 19 to 31.
Compared on 3 doses of Sertraline with placebo and Zimelidine (another SSRI)

Doses	S100,	S200,	S400,	Plac	Z
Nausea	2	5	10	0	0
Dizziness	2	5	4	1	0
Agitation	0	3	5	0	1
Nervous	0	1	0	0	0
Yawning	2	3	1	0	0
Hypertonia	0	2	4	0	0
Tremor	1	2	4	0	0
Tiredness	1	3	3	0	0
Trismus	0	0	3	0	0
Masseter C	0	1	2	0	0
Psych	3	7	5	0	0
Neuro	3	8	7	0	3

Restlessness is recoded by Pfizer monitors as agitation
And occurs in moderate to severe levels
Present in 50% of 400mg dose.

The investigators report:
"Significant deterioration in wellbeing in 4th to 8th hour.
Affectivity worsened over same period – Saletu et al "

"Sertraline was associated with dose related side effects which in decreasing order of frequency were nausea, dizziness, agitation, fatigue, vomiting, tremor, hypertonia of the masseter muscles and yawning. The severity of the side effects was also dose related".

Grunberger J, Saletu B, 1980. Determination of pharmacodynamics of psychotropic drugs by psychometric analysis. Prog Neuropsychopharmacol 4, 417-434.

"Both the 200 and 400 mg doses could be considered poorly tolerated by volunteers"

Most frequent side effects were restlessness and tremor. These somatic complaints lasted sometimes up to 48 hours after single dosing.

Marked restlessness, tremor, trismus

This study was also published in
Saletu B, Grunberger J (1988). Drug profiling by computed electroencephalography and brain maps with special consideration of sertraline and its psychometric effects. J Clin Psychiatry 49: 8 (suppl), 59-71.

This latter report makes it clear that using a von Zerssen scale for subjectively experienced well being a “significant deterioration occurred between 4 and 8 hours with sertraline 200 and 400 mg ($p < 0.01$)”.

On affectivity “both sertraline 200 and 400 mg caused deterioration ($p < 0.05$)”.

Healy Zoloft Healthy Volunteer Study

There is one more study to add. This was published as:

Healy D (2000). Emergence of antidepressant induced suicidality. Primary Care Psychiatry 6, 23-28.

It is attached as Appendix 3b