Spitzer vs. GlaxoSmithKline

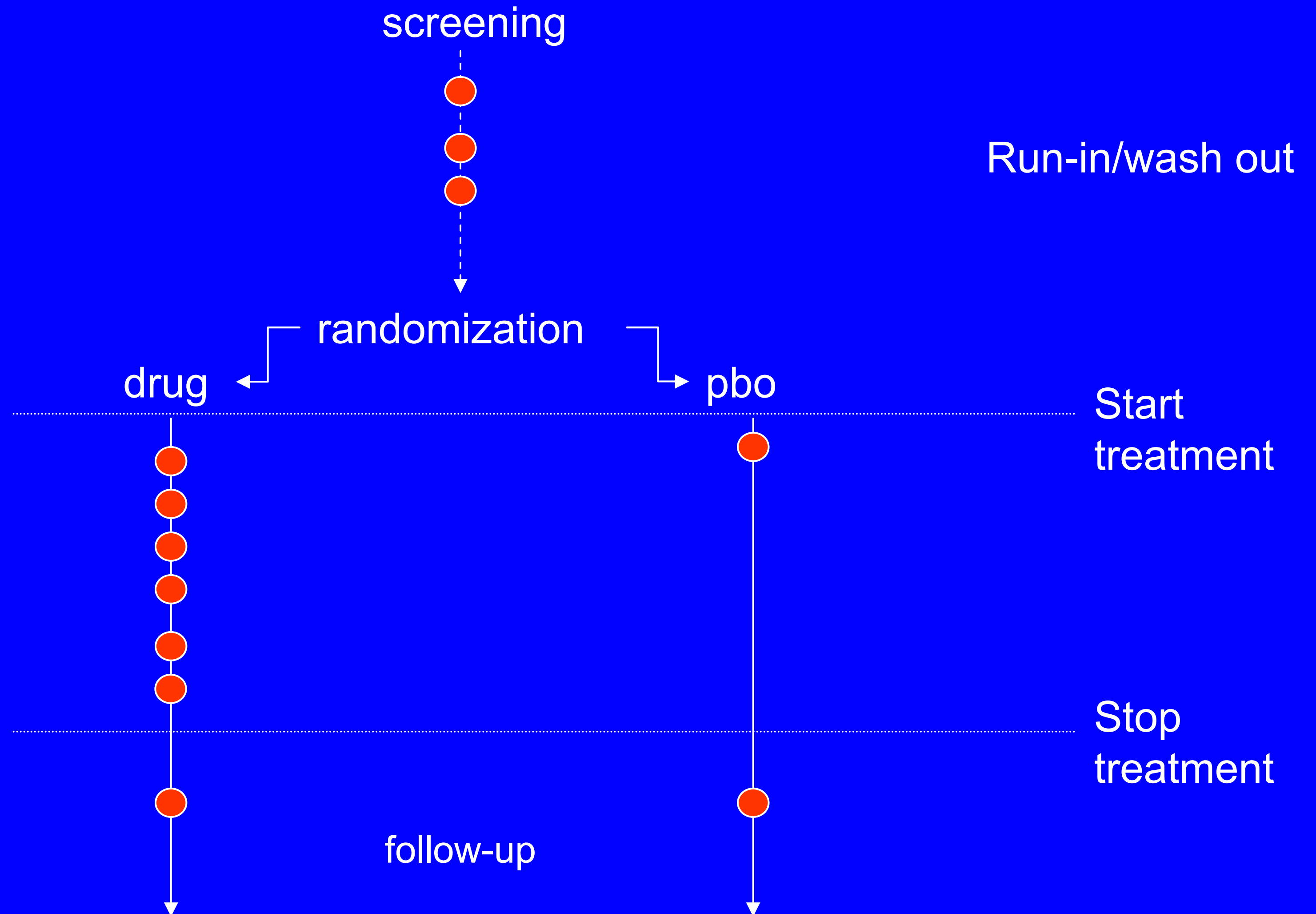
In 2004 the Attorny General of New York State sued GlaxoSmithKline for ’repeated and persistent fraud’.

FLUOXETINE – PAROXETINE - SERTRALINE ADULT TRIALS

Occurrence of suicidal acts

1

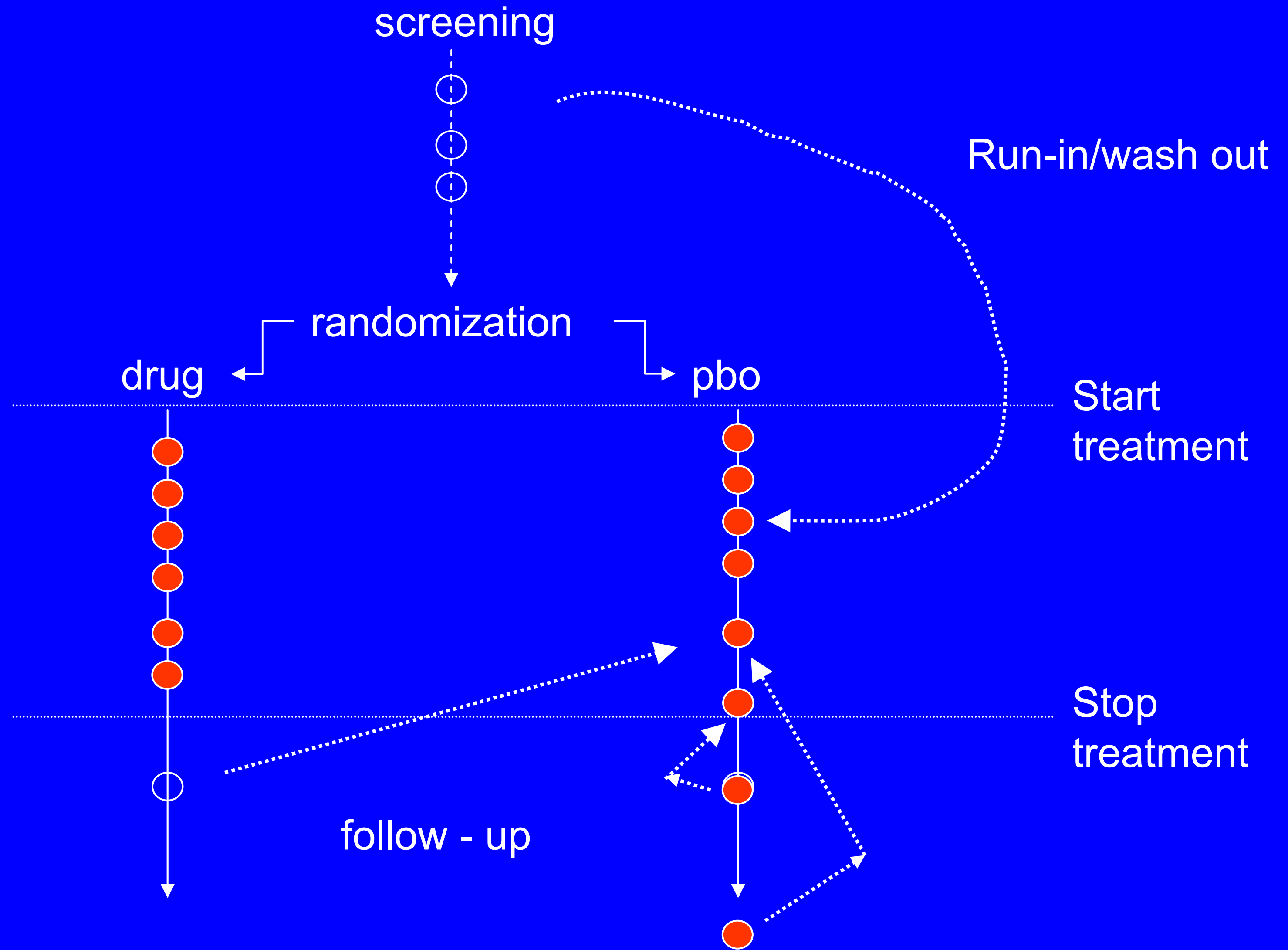
Healy BMJ 2006, slide from Healy



FLUOXETINE – PAROXETINE - SERTRALINE ADULT TRIALS

Reporting of suicidal acts

Healy BMJ 2006, slide from Healy



Selective reporting of trial 329 (paroxetine vs placebo in adolescents), GlaxoSmithKline

”paroxetine is generally well tolerated and effective for major depression in adolescents” (Martin Keller et al., published paper)

One of the most cited papers (184 by 2010).

GSK to its sales force: ”REMARKABLE Efficacy and Safety”

Documents obtained during litigation reveal that study 329 was negative for efficacy on all 8 protocol specified outcomes and positive for harm.

The paper was ghostwritten but had 22 authors

(Jureidini, Int J Risk Safety Med 2008:73)

(Jureidini, Accountability in Research 2011)

Selective reporting of trial 329 (paroxetine vs placebo in adolescents), GlaxoSmithKline

"originally we had planned to do extensive media relations surrounding this study until we actually viewed the results. Essentially the study did not really show Paxil was effective in treating adolescent depression, which is not something we want to publicize"

(Spielmans, Bioethical Inquiry 2010)

Selective reporting of trial 329 (paroxetine vs placebo in adolescents), GlaxoSmithKline

Outcome measures (significant results in **bold**); ordering of outcome measures is from originals

Protocol (1993, 1996) [12]	p	Final paper (2001) [5]	p
*Change in HAM-D total score	0.13	**HAM-D ⩽ 8**	**0.02**
*Responders (HAM-D ⩽ 8 or reduced by ⩾50%)	0.11	*Responders (HAM-D ⩽ 8 or reduced by ⩾50%)	0.11
Depression scale of K-SADS-L	0.07	**HAM-D depressed mood item**	**0.001**
Mean Clinical Global Improvement (CGI) score	0.09	**K-SADS-L depressed mood item**	**0.05**
Autonomous function checklist	0.15	**CGI 1 or 2**	**0.02**
Self-perception profile	0.54	Depression scale of K-SADS-L	0.07
Sickness impact scale	0.46	Mean CGI	0.09
Relapse during maintenance	0.24**	*HAM-D total score	0.13

*Protocol specified primary outcomes. **Not published, calculated by us, trend favours placebo.

Compared to protocol, at least 19 additional outcomes were tested

Keller et al. J. Am. Acad. Child Adolesc. Psychiatr. **40** (2001), 762–772

Selective reporting of trial 329 (paroxetine vs placebo in adolescents), GlaxoSmithKline

Keller: ”depression-related variables were declared a priori.”

No document prior to eight months after breaking the blind mentions the K-SADS depression item as an outcome measure.

The term ’primary outcome’ replaced by ’ depression-related outcome’

Selective reporting of trial 329 (paroxetine vs placebo in adolescents), GlaxoSmithKline

Serious adverse effects: 11/93 on paroxetine vs 2/87 on placebo ($p=0.01$)

5 suicidal thoughts and behaviour called ”emotional lability”

3 additional cases of suicidal ideation or self-harm called ”hospitalisation”

Early drafts of the paper prepared for JAMA did not discuss SAEs at all

Later draft: worsening depression, emotional lability, headache, and hostility were considered related or possibly related to treatment

Published: only headache (1 patient) was considered by the treating investigator to be related to paroxetine treatment

What the unpublished study report showed: 8 vs 1 suicidal ($P=0.035$)

Selective reporting of GlaxoSmithKline's trials

GSK had decided not to publish clinical trials from the late 1990's with mixed or negative results: little effect on depression and increased suicidal behaviour.

A 1998 memo from the Central Medical Affairs team said: "It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine."

Kondro CMAJ 2004

Internal industry documents

Quetiapine (Seroquel), AstraZeneca

Presentation at a congress and press release: Meta-analysis of four trials, quetiapine is significantly better than haloperidol.

Internal document: quetiapine possesses *weaker* efficacy than haloperidol.

Negative trials called ”buried trials” in internal emails.

Trial showing haloperidol was best published showing quetiapine was best.

Spielmans, Bioethical Inquiry 2010

Internal industry documents

AstraZeneca, Seroquel Speakers Slide Kit

"Long-term Seroquel has neutral effect on weight"

"Seroquel - weight neutral at all doses".

Journal publication: concluded that based on data from clinical trials with patients with schizophrenia, quetiapine had a neutral effect on weight.

Internal documents

"the incidence rate in adult patients with weight gain ≥7% in all trials was 18.2%"

In placebo-controlled trials, the relative risk of clinically significant weight gain was 2.5.

Spielmans, Bioethical Inquiry 2010

Internal industry documents

Letter from psychiatrist (on Lilly's speaker's bureau) to Lilly about off-label use

"... Once the ground is extensively plowed with good credible clinical information, not limited by the GPP [Good Promotional Practice] guidelines that restrict information to schizophrenia and acute mania, then (perhaps) turning the sales force loose may be appropriate. I believe one of my strengths is in taking scientific information and placing it in a clear, clinically useful format ... Lilly could use someone with a strong clinical background but with strong marketing instincts to assist them on this one."

Spielmans, Bioethical Inquiry 2010

Internal industry documents

Our customers tell us today that diabetes is not an issue!

Therefore, with most customers we will address the diabetes concern only when it arises (as follows):

1. Have you seen it or heard it?
2. Share information in context of the overall safety profile and give the "comparable rates message" with the correct ordering of message elements and tone.
3. Probe for agreement and create action around efficacy & safety.
4. Probe on follow-up calls to make sure the objection is handled. "Last time we talked you asked if Zyprexa causes diabetes. I showed you information that the risk for Zyprexa patients is comparable to other agents. I want to check your confidence in Zyprexa's safety profile."

Company Confidential
Copyright ©[illegible] Eli Lilly and Company

Fig. 6 Olanzapine diabetes sell sheet excerpt

Spielmans, Bioethical Inquiry 2010

Internal industry documents

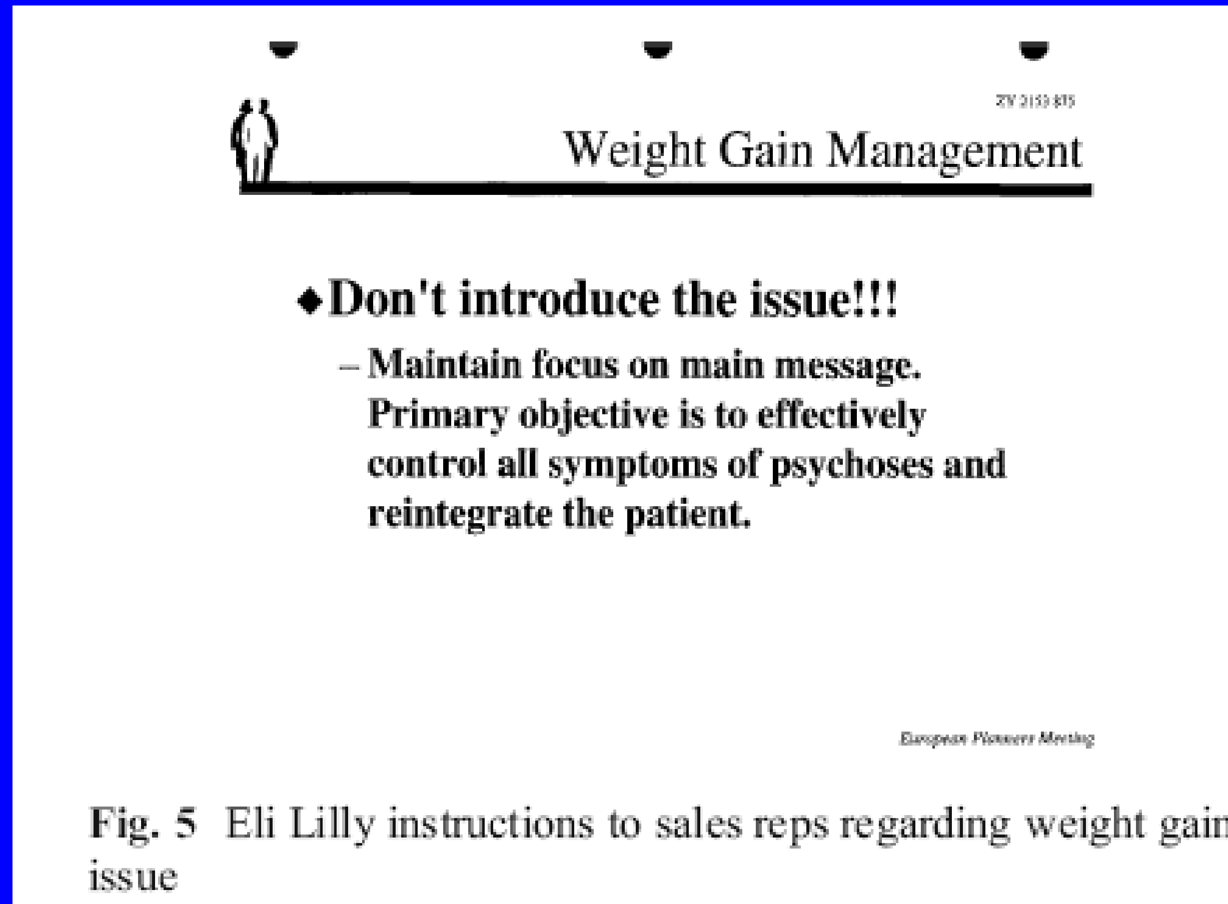


Fig. 5 Eli Lilly instructions to sales reps regarding weight gain issue

Spielmans, Bioethical Inquiry 2010

Internal industry documents

Internal Lilly email about Wishing/Goldstein articles

I do have concerns regarding making any connections between olanzapine-induced weight gain and hyperglycemia. Therefore, in my opinion, I would not include your following statement: “Patients who gain weight may develop insulin resistance which may lead to hyperglycemia and diabetes”

Spielmans, Bioethical Inquiry 2010

Internal industry documents

Lilly message to sales reps

Market research has shown that ALL of our competitors are talking about a supposed link between hyperglycemia/diabetes and ZYPREXA. This is one of the biggest issues we face in the marketplace. The exciting thing is that we have more data than ever to back up our story of "comparable rates of hyperglycemia and diabetes across psychotropic agents." It is critical to our success that we share this information with physicians

Spielmans, Bioethical Inquiry 2010

Internal industry documents

Lilly, disease mongering

"Global Zyprexa Bipolar Forecast": sales projections for the year 2000 would increase more than fourfold if Zyprexa could be viewed as a ...MOOD-STABILIZER rather than as a risperdal-like antipsychotic

A true mood stabilizer will work in acute manic episodes without inducing depression, acute depression without inducing mania, and protect the patient from future episodes of mania or depression. (the same document indicated the company did not have the data to support such a goal.)

Spielmans, Bioethical Inquiry 2010

Internal industry documents

Lilly, disease mongering

Expand our market by redefining how primary care physicians identify, diagnose and treat complicated mood disorders.

Physicians in primary care did not typically treat bipolar disorder and used antipsychotic medications infrequently, partially due to safety concerns. The company, however, aimed to "change their paradigm"

Spielmans, Bioethical Inquiry 2010

Internal industry documents

Lilly, disease mongering

Part of this marketing campaign was to broaden the concept of bipolar disorder to include “complicated mood,” comprised of some combination of anxiety, disruptive sleep, irritability, and mood swings. This new type of patient was a source of “untapped growth potential” for the drug. Additionally, fictional patient vignettes were created for sales reps that highlighted possible bipolar disorder or “complicated mood” in cases of relatively minor mood instability that did not meet current diagnostic manual (DSM-IV, ICD-10) criteria for bipolar disorder I diagnosis.

Spielmans, Bioethical Inquiry 2010