Antipsychotics – psychiatry's poster child

Chlorpromazine launched 1954. At first:

Chemical lobotomy or straitjacket, no specific antipsychotic properties

One year later, the hype was extreme. Harold Himwich, president of the US Society of Biological Psychiatry, came up with the totally weird idea that antipsychotics work like insulin for diabetes.

"It emptied the asylums" (not true)

Double-blind trial: NIMH investigators who had not been blinded effectively saw the exact opposite of what is actually true when they medicate patients: reduced apathy, improved motor movement , less indifference.

Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press; 2015.

Treatment for schizophrenia

2,000 trials in schizophrenia

”Half a century of studies of limited quality, duration, and clinical utility leave much scope for well planned, conducted, and reported trials”

(BMJ 1998;317:1181)

Do antipsychotics work?

They are not specific drugs ("anti" is a misnomer)

The placebo controlled trials are highly flawed:

- lack of blinding
- cold turkey in the placebo group = iatrogenic harm

Despite these flaws, effect in recent submissions to the FDA:

- 6 points on the Positive and Negative Syndrome Scale (PANSS)

The minimally clinically relevant change is 15 points

The schizophrenia diagnosis can be wrong in over 50% of cases

Khin NA, et al. J Clin Psychiatry 2012;73:856–64.

Leucht S, et al. Neuropsychopharmacology 2006;31:2318-25.

Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press; 2015.

Lethal trial design

The cold turkey design is lethal.

One in every 145 patients who entered the trials for risperidone (Janssen), olanzapine (Eli Lilly), quetiapine (AstraZeneca) and sertindole (Lundbeck) died, but none of these deaths were mentioned in the scientific literature, and the FDA didn't require them to be mentioned.

Whitaker R. Mad in America. Cambridge: Perseus Books Group; 2002

Antipsychotics kill people

Trials in schizophrenia are grossly unreliable, cold turkey on placebo

Meta-analysis of trials in patients with Alzheimer's disease or dementia:

- aripiprazole (Abilify)
- olanzapine (Zyprexa)
- quetiapine (Seroquel
- risperidone (Risperdal)

For every 100 patients treated, there was one additional death on the drug (3.5% versus 2.3% died, P = 0.02).

Schneider LS, et al. JAMA 2005;294:1934–43.

Antipsychotics cripple people

Irreversible brain damage, in a dose-related fashion

Less chance of getting back to a normal life

Dependency, abstinence symptoms

Supersensitivity psychosis

And a lot else … some of the most toxic drugs ever made, apart from chemotherapy for cancer

Whitaker R. Mad in America. Cambridge: Perseus Books Group; 2002.

Whitaker R. Anatomy of an Epidemic. New York: Broadway Paperbacks; 2010.

Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press; 2015.

A huge, but deeply flawed Cochrane review

Chlorpromazine versus placebo for schizophrenia (55 trials; 5,506 patients)

Abstract: "Akathisia did not occur more often in the chlorpromazine group than placebo" (no reservation).

The largest trial that contributed data found *significantly less* akathisia on drug than on placebo (relative risk 0.57, 95% CI 0.37 to 0.88).

Antipsychotics *cause* akathisia; placebo *cannot* cause akathisia.

This result speaks volumes about how flawed trials in schizophrenia are.

What was seen in the placebo group were cold turkey symptoms *caused* by withdrawal of the antipsychotics the patients had received before randomisation.

Adams CE, et al. Cochrane Database Syst Rev 2014;1:CD000284.

Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press; 2015.

A much better Cochrane review

Antipsychotic medication for early episode schizophrenia

A review of studies “with a majority of first and second episode schizophrenia spectrum disorders” (thus, still flawed)

”available evidence does not support a conclusion that antipsychotic treatment in an acute early episode of schizophrenia is effective”

”The use of antipsychotic medications for millions of people with an early episode appears based on the evidence for those with multiple previous episodes”

Bola J, et al. Cochrane Database Syst Rev 2011;6:CD006374.

Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People’s Press; 2015.

Long-term results of maintenance trial

- 128 remitted first-episode psychotic patients
- randomized to dose reduction/discontinuation or maintenance for 2 years, thereafter Tx as decided by the clinicians
- 103 patients were located 7 years after randomisation

	2 yr	7 yr
Relapse	43% DR vs 21% M	62% DR vs 69% M
Recovery (main outcome)		40% DR vs 18% M

Dose in last 2 years was 64% higher in maintenance group

Stopped drug completely at 7 years: 11 versus 6 patients

Wunderink et al., *JAMA Psychiatry. doi:10.1001/jamapsychiatry.2013.19*

Why don’t we use benzodiazepines?

Psychiatrists have failed to live up to their professional responsibility by neglecting to perform head-to-head trials with antipsychotics.

In 1989, 35 years after chlorpromazine came on the market, only two trials had compared the two types of drugs, and they produced similar improvements.

There are now more trials. Cochrane review: sedation occurred significantly more often on benzodiazepines (14 trials).

Dold M, et al. Cochrane Database Syst Rev 2012;11:CD006391.

Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People’s Press; 2015.

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

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

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

Spielmans, Bioethical Inquiry 2010

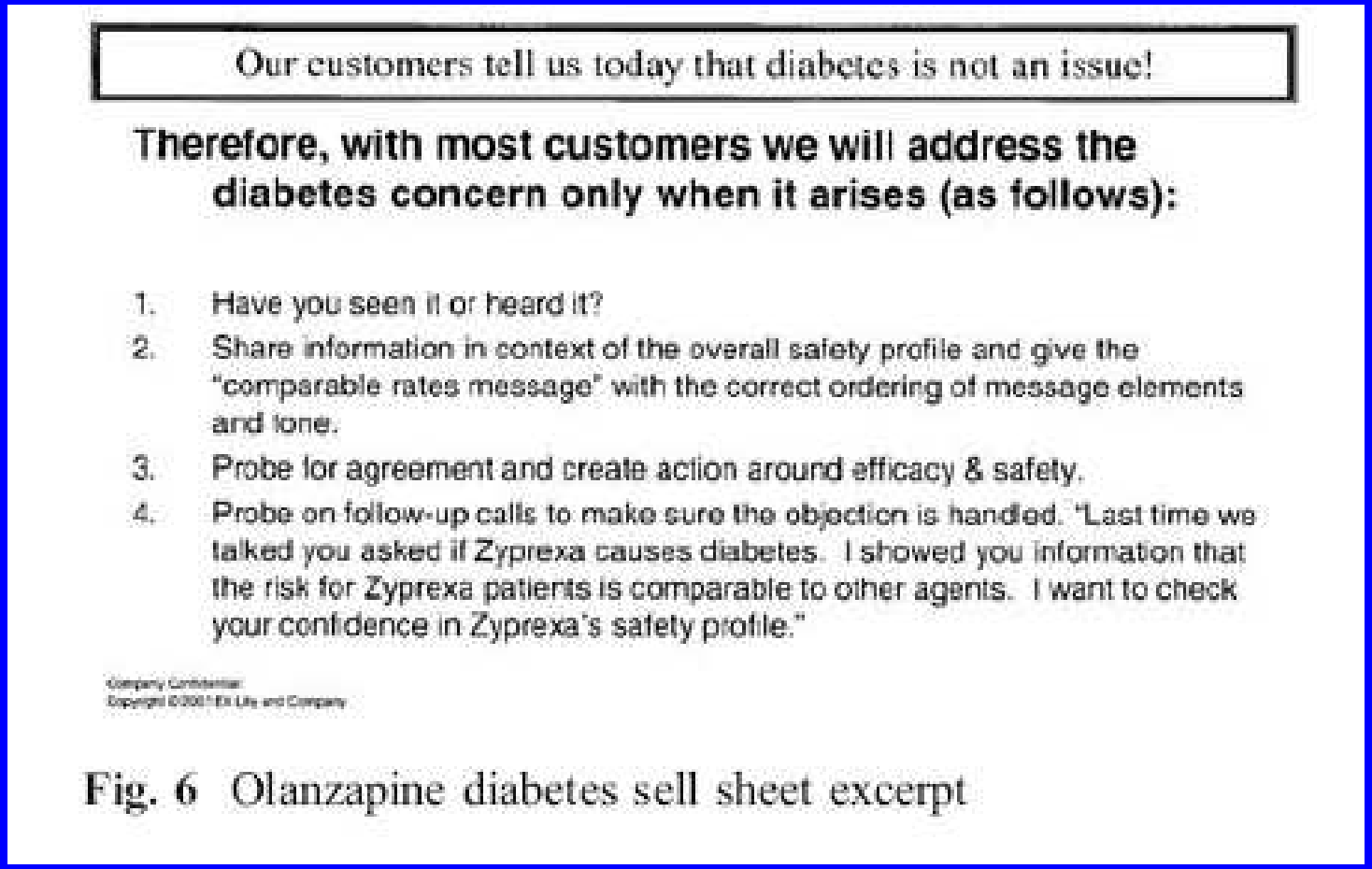
Internal industry documents

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."

Fig. 6 Olanzapine diabetes sell sheet excerpt

Spielmans, Bioethical Inquiry 2010

Internal industry documents

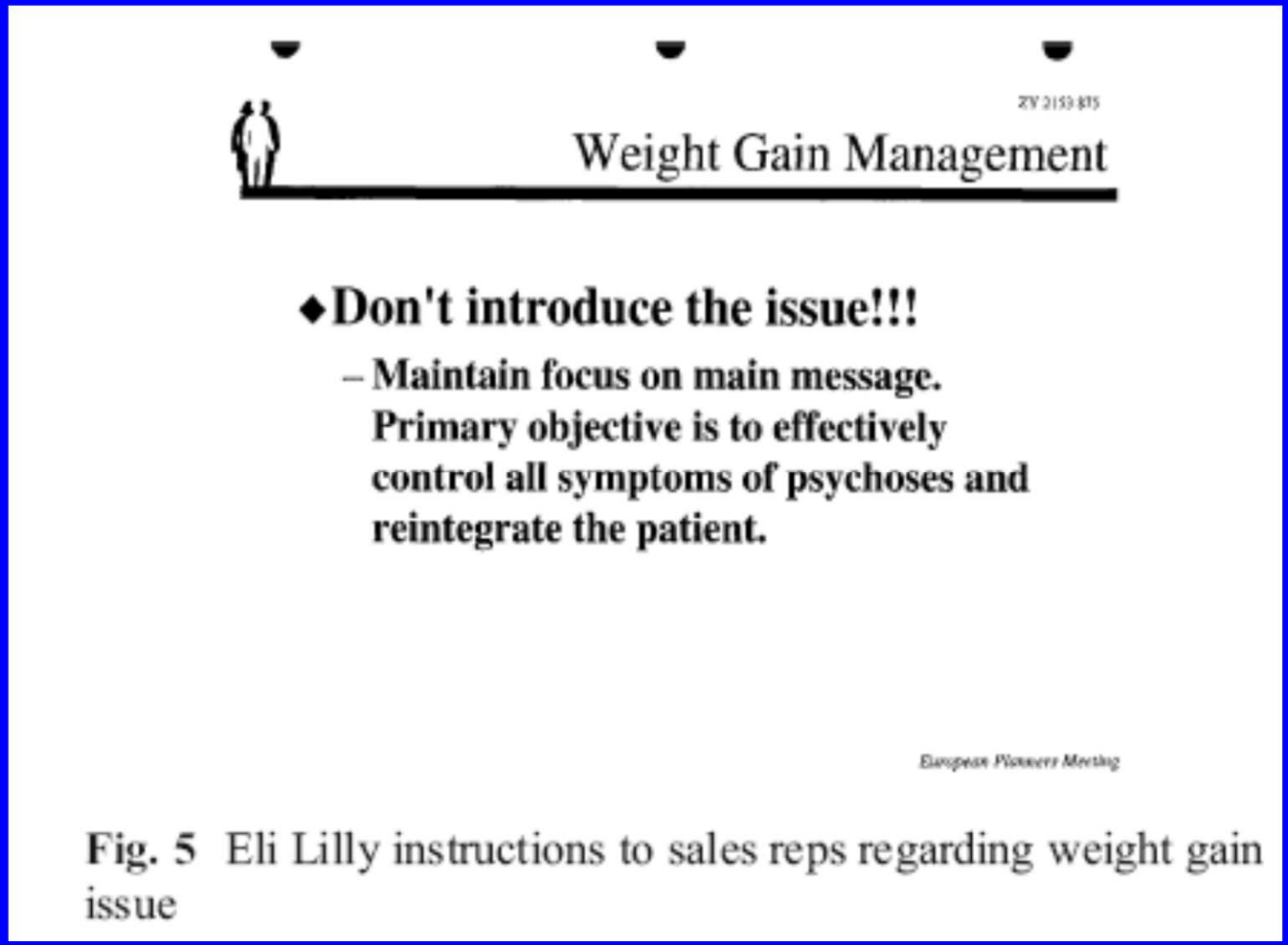


Fig. 5 Eli Lilly instructions to sales reps regarding weight gain issue

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

Treatment for schizophrenia

”It goes completely wrong, when PG mentions olanzapine. Modern antipsychotics should, in particular, be used for chronic treatment”

(Authors from Drug Agency, Ugeskr Læger 2005;167:2307)

Trial in 1493 patients, 5 drugs, sponsored by National Institute of Mental Health

Olanzapine and perphenazine: trade-offs, not clear that one is better than the other

(Lieberman, NEJM 2005;353:1209)