Access to data from regulatory authorities

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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)

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"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)

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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 $\leqslant 8$**	**0.02**
*Responders (HAM-D $\leqslant 8$ or reduced by $\geqslant 50\%$)	0.11	*Responders (HAM-D $\leqslant 8$ or reduced by $\geqslant 50\%$)	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.

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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’

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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

Publication bias, Eyding, IQWiG, BMJ 2010:c4737

Data on 74% (3033/4098) of patients were unpublished

	Reboxetine (n/N)	Placebo or selective serotonin reuptake inhibitor (n/N)	Odds ratio (95% CI)	Odds ratio (95% CI)	Ratio of odds ratios; published:unpublished (95% CI)	Publication bias (%)
Reboxetine v placebo						
Remission						
Published (1)	60/126	34/128		2.51 (1.49 to 4.25)		
Unpublished (6)	395/938	379/930		1.06 (0.88 to 1.28)	2.37 (1.36 to 4.13)	115
Total (7)	455/1064	413/1058		1.17 (0.91 to 1.51)		
Response						
Published (1)	70/126	43/128		2.47 (1.49 to 4.11)		
Unpublished (6)	469/938	439/930		1.12 (0.93 to 1.35)	2.21 (1.28 to 3.79)	99
Total (7)	539/1064	482/1058		1.24 (0.98 to 1.56)		
Patients with adverse events						
Published (2)	108/154	91/156		2.67 (0.52 to 13.79)		
Unpublished (6)	839/979	713/959		2.15 (1.66 to 2.80)	1.24 (0.24 to 6.53)	25
Total (8)	947/1133	804/1115		2.14 (1.59 to 2.88)		
Withdrawal owing to adverse events						
Published (2)	15/154	16/156		0.95 (0.45 to 1.99)		
Unpublished (6)	122/979	48/959		2.61 (1.79 to 3.80)	0.36 (0.16 to 0.84)	-57
Total (8)	137/1133	64/1115		2.21 (1.45 to 3.37)