“There is as much difference between us and ourselves as between us and others.”

Michel de Montaigne, essayist (1533-1592)
Mitigating Bias in Literature Evaluation

Learning Objectives
Practice approaches & strategies to mitigate bias in literature evaluation

Literature Evaluation

“Science is at once the most questioning and the most skeptical of activities and also the most trusting. It is intensely skeptical about the possibility of error, but totally trusting about the possibility of fraud.”
Arnold Relman, 1989

Study 329… (Keller et al, 2001)
Paroxetine vs imipramine vs placebo

- 275 adolescents, 8 wks, DBRCT
- Two primary outcomes:
  - Change in total HAM-D
  - Proportion of responders (decr. >50% or <8)

...Study 329…
“no significant difference between the paroxetine and placebo groups on any of the eight pre-specified outcome measures”

Jureidini, 2008
Internal GSK memo re: Studies 329 & 377

• “it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine”

• “effectively manage the dissemination of these data in order to minimise any potential negative commercial impact”

Kondro, 2004

Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial

Abstract conclusion: “Paroxetine is generally well tolerated and effective for major depression in adolescents.”

Methods…

...Methods...

...Methods...

...Methods
Abstract & Introduction...

...Abstract & Introduction

...Study 329...

• New outcome measures – at least 19 – after breaking the blind
• Many tested and rejected
• 4 out of 27 outcome measures positive

Jureidini et al., 2008

...Study 329...

Jureidini et al., 2008

...Study 329...

Memorandum from Paxil Product Management to “all sales representatives selling Paxil”: “This ‘cutting edge,’ landmark study is the first to compare efficacy of an SSRI and a TCA with placebo in the treatment of major depression in adolescents. Paxil demonstrates REMARKABLE Efficacy and Safety in the treatment of adolescent depression”

Jureidini et al., 2008
“To have the placid faith of the simple believer, instead of the fighting faith of the aggressive doubter, has ever been our besetting sin in the matter of treatment.

In the progress of knowledge each generation has a double labour – to escape from the intellectual thralls of the one from which it has emerged and to forge anew its own fetters.”

William Osler, address to OMA, 1909
New outcome measures – at least 19 – after breaking the blind
Many tested and rejected
4 out of 27 outcome measures positive

Jureidini et al, 2008
### Table 2
Adverse events documented in SKB’s final report of study 329 [14]

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Paroxetine $(N = 93)$</th>
<th>Placebo $(N = 87)$</th>
<th>$p^{\wedge}$</th>
<th>Source table</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious#</td>
<td>11 (12%)</td>
<td>2 (2.3%)</td>
<td>0.01</td>
<td>48, p. 109</td>
</tr>
<tr>
<td>Severe##</td>
<td>27 (29%)</td>
<td>15 (17%)</td>
<td>0.06</td>
<td>14.3.1, pp. 231–238</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>6* (6.5%)</td>
<td>0</td>
<td>0.004</td>
<td>48, p. 109</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>56 (60%)</td>
<td>29 (33%)</td>
<td>0.001</td>
<td>14.2.1, p. 227</td>
</tr>
<tr>
<td>Severe**</td>
<td>17 (18%)</td>
<td>4 (4.6%)</td>
<td>0.003</td>
<td>14.3.1, pp. 231–238</td>
</tr>
<tr>
<td>Requiring withdrawal</td>
<td>8 (8.6%)</td>
<td>2 (2.3%)</td>
<td>0.056</td>
<td>49, p. 111</td>
</tr>
<tr>
<td>Leading to dose reductions</td>
<td>8 (8.6%)</td>
<td>2 (2.3%)</td>
<td>0.056</td>
<td>46, p. 105</td>
</tr>
</tbody>
</table>

$^{\wedge}$ Calculated by us; # ‘resulted in hospitalisation, was associated with suicidal gestures, or was described by the treating physician as serious’ [5]; ## ‘incapacitating and prevents normal everyday activities’ [14, p. 565]; * stated as 7 in published paper; ** stated as 16 for paroxetine and 3 for placebo in Table 44, p. 101.

Jureidini et al, 2008