Orygen

The National Centre of Excellence in Youth Mental Health

Newer antidepressants for child and adolescent depression

The role of industry in research

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Youth depression

Context

- Depressive disorders account for the greatest global burden of disease in young people
- In NZ, 18.3% of female and 8.9% of male adolescents demonstrate clinically significant depression
- Associated with poor educational/vocational outcomes, welfare dependency, diminished number and poor quality of friendships and intimate relationships
- Associated with increased risks of self-harm and suicide

Antidepressants for youth depression

Guidelines

- CBT or IPT as first line intervention for adolescents with major depression
- Fluoxetine considered for acute, short-term reduction of depressive symptoms in adolescents with moderate to severe major depressive disorder, where psychological therapy has not been effective, is not available or is refused, or if symptoms are severe
- CBT may be added to/continued with SSRI therapy, to reduce the risk of suicidal thinking and improve functioning in adolescents with major depressive disorder
- Symptoms and risk must be monitored

Antidepressants for youth depression

Guideline adherence

- Assessment and recording of depression severity to ensure appropriate treatment planning was not systematic nor consistent
- 74.5% were prescribed an antidepressant before an adequate trial of psychotherapy
- 92% of first line prescriptions for those aged 18 years or under who were previously antidepressant-naïve was for fluoxetine
- 35% monitored for depression symptom improvement
- 30% monitored for SRBs

Antidepressants for youth depression

Percentage change in dispensing from 2009 to 2012

Antidepressant	3-9	10-14	15-19	20-24
ALL	28.3	35.5	31.9	19.5
SSRI	49.1	42.2	24.4	5.4
SNRI	69.9	58.9	50.9	38.2
NaSSA	23.4	1.9	35.6	19.7
TCA	-5.2	0.7	21.7	15.0
MAOI	N/A	-25.3	-18.7	-18.8

SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin norepinephrine reuptake inhibitors; NaSSAs: noradrenergic and specific serotonergic reuptake inhibitors; TCAs: tricyclic antidepressants; MAOIs: monoamine oxidase inhibitors

The Cochrane Review

First published 2007; updated 2012

- 2007: 12 trials; 10 with data on response; 9 with data on Suicide Related Behaviours; SRBs
- 2012: 19 trials; 14 with CDRS-R data; 17 with data on SRBs
- 2012 included venlafaxine, duloxetine (both serotonin norepinephrine reuptake inhibitors) & mirtazapine (tetracyclic antidepressants; TeCAs)
- 2012: subgroup analysis based on the individual compounds to examine if the effect of newer generation antidepressants was modified by individual drug

The Cochrane Review

Included trials

- No trials were at low risk of bias (missing information meant unclear ratings), high drop out rates
- Issues regarding measurement instruments and clinical usefulness of outcomes
- Trials excluded young people at high risk of suicide and with comorbidity
- Poor reporting of adverse outcomes

Industry Funding in the Included Trials

Study ID	Drug	Funding
Almeida-Montes 2005	Fluoxetine	Eli Lilly provided fluoxetine and placebo
Berard 2006 (377)	Paroxetine	SmithKlineBeecham
Emslie 1997	Fluoxetine	National Institutes of Mental Health (NIMH) (no other declaration)
Emslie 2002	Fluoxetine	Eli Lily
Emslie 2006 (701)	Paroxetine	GlaxoSmithKline
Emslie 2007	Venlafaxine	Wyeth Research
Emslie 2009	Escitalopram	Forest laboratories
Keller 2001 (329)	Paroxetine	GlaxoSmithKline
Mirtazapine Trial 1	Mirtazapine	Organon International
Mirtazapine Trial 2	Mirtazapine	Organon International
Paroxetine Trial 1 (Japan)	Paroxetine	GlaxoSmithKline
Simeon 1990 (no outcome data)	Fluoxetine	Not stated
TADS 2004	Fluoxetine	NIMH; Lilly Inc provided fluoxetine and matching placebo under an independent educational grant to Duke University
Von Knorring 2006	Citalopram	Pharmaceutical company not stated
Wagner 2004	Citalopram	Forest Laboratories and Lexicon Pharmaceuticals
Wagner 2006	Escitalopram	Forest Laboratories
Wagner Trial 1 & 2 (2003)	Sertraline	Pfizer

Pharmaceutical funding

Selective reporting

Study 329; Keller 2001 (Paroxetine)

- pre-specified primary efficacy variables :
  - Change in Hamilton Depression Scale (HAM-D) score; &
  - Response (HAM-D score ≤8 or ≥50% reduction in baseline HAM-D)
- Keller et al. claimed efficacy for paroxetine on the basis of 'response' (definition changed : HAM-D to below 8)
- Did not highlight that change in HAM-D score (also a primary outcome) did not show significant improvement
- No difference in paroxetine and imipramine from placebo for any measure on basis of the pre-defined outcome 'response'

Selective reporting

Keller response

- **It still provides a strong "signal" for efficacy**
- **Suggest that Jureidini and Tonkin have accused the reviewers and editor were 'not up to the task' and that the** authors **'swerved from their moral and scientific duty under the influence of the pharmaceutical industry'**

Medical ghost writing

Keller et al 2001 an example of a ghost written trial

- A well-known and respected academic physician (a key opinion leader) is cited as the author of a publication written by an author employed by a pharmacetuical company
- One study (Healy & Cattell 2003) showed that ghost written articles of sertaline were:
  - were published in more prestigious journals
  - were more highly cited
  - contained significant discrepancies between raw and published data

Healy D & Cattell D (2003). Interface between authorship, industry and science in the domain of therapeutics. British Journal of Psychiatry 183: 22-27

The RIAT initiative

Restoring Invisible and Abandoned Trials (RIAT) initiative

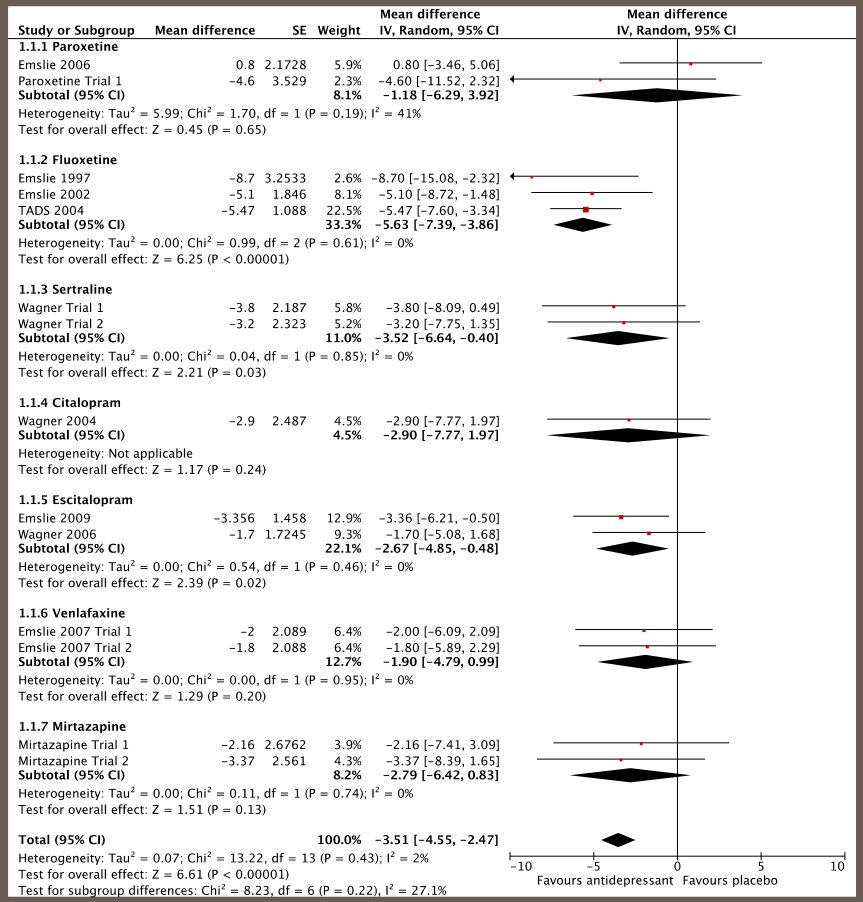
- Called on funders and investigators of unpublished or misreported trials to publish undisclosed outcomes or correct misleading publications
- Trial 329 (Keller 2001) is one example of a misreported trial that they are pursuing
- Concerns that group analysing study 329 data are not 'independent' (they are the group who originally wrote the letter to the editor).

The Cochrane Review

Our findings: 2012 results

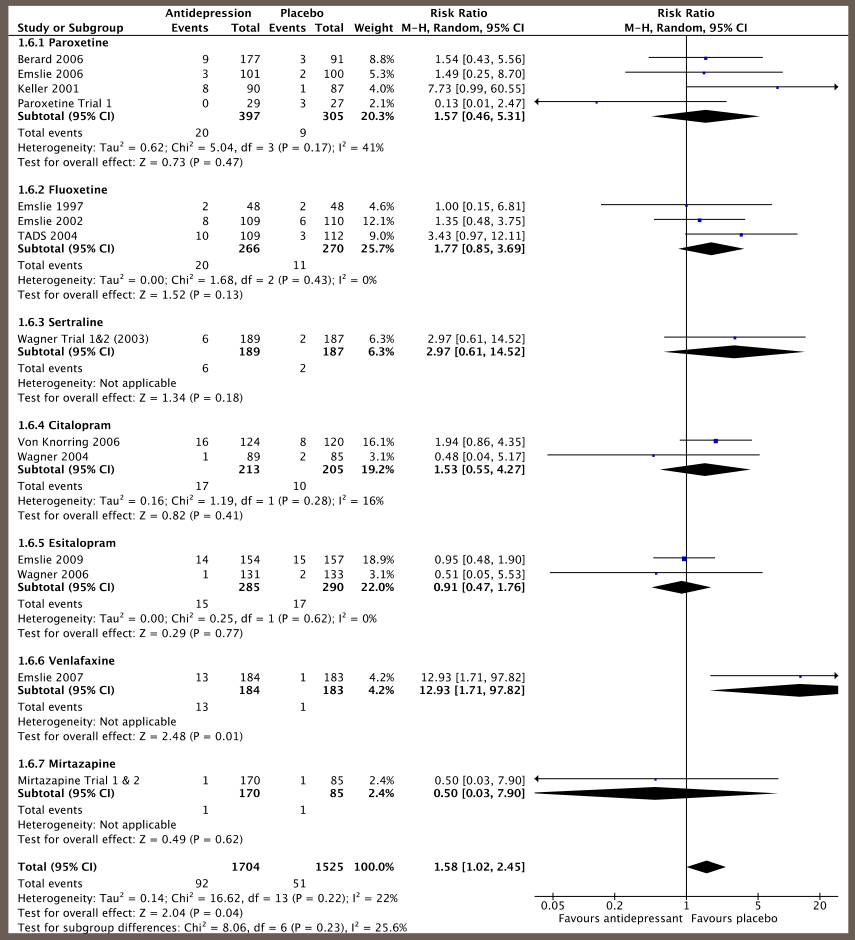
- 19 trials (14 with CDRS-R data; 17 with data on Suicide Related Behaviours; SRBs)
- Those on antidepressants had:
  - Lower depression scores (3.51; CI -4.55, -2.47, on a scale from 17 to 113)
  - Increased remission rates (increased from 380 per 1000 to 448 per 1000)
  - Increased risk (58%) of SRBs (increased from 25 per 1000 to 40 per 1000)
- No evidence that the magnitude of treatment effect is modified by individual drug class

Our results



Depressive symptom severity post intervention

Our results



Suicide related behaviours post intervention

The Cochrane Review

Our conclusions

- Caution required interpreting the results: 1. methodological limitations (both internal and external validity); 2. size and clinical meaningfulness of results
- Given risks of untreated depression, if a decision to use medication is agreed (on the basis of sharing accurate information regarding uncertainty about risk and benefits), fluoxetine might be first choice given guideline recommendations
- Clinicians need to keep in mind the increased risk of SRBs

The Cochrane Review

Response to our findings

- "Examining the role of these medications using meta-analytic techniques has been popular in recent years invariably from a rather negative perspective and without reference to the relative potency of treatments (pharmacological and psychological)"
- "Hetrick et al findings need to be set in context"
  - "considerable evidence for efficacy…across the lifespan"
  - Neurobiology/mechanism of change is the same across the lifespan so why wouldn't they work?
  - Large placebo effect rather than a reduced treatment effect with larger placebo-SSRI differences in real-world patients
  - SSRIs probably work of subgroups e.g. moderate to severe depression

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Response to our findings

- Suicide risk is undetectable; good clinical care/CBT eliminates it; use of SSRIs has reduced suicide rate
- The efficacy of psychotherapy is similar (although they do argue that there should be greater availability of this)
- There are no alternatives
- Stepped care; watchful waiting; specialist psychological treatments; consideration of fluxoetine after 4 to 6 weeks