Rethinking Antidepressant Use in Children and Adolescents

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Presenter (M Al-Sukhni) Disclosures

- I have no current or past relationships with commercial entities
- I have received no speaker's fee for this learning activity

Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization

Learning Objectives

- To review recent evidence regarding use of antidepressants in children and adolescents
- To reflect on the validity and rigour of results from pediatric antidepressant trials

Major Depression in Youth

- Prevalence: 2.8% in children; 5.6% in adolescents (Costello 2006)
- Clinical presentation similar as in adults
- Potential for serious consequences if persistent

Treatment Strategies

- Non-pharmacological
  - Cognitive behavioural therapy
  - Interpersonal therapy
  - Psychodynamic therapy
  - School interventions
  - Psychoeducation
- Pharmacological
  - Selective serotonin reuptake inhibitor

Guideline Recommendations

- National Institute for Health and Care Excellence (2015)
- American Academy of Child and Adolescent Psychiatry (2007)
- Royal Australian and New Zealand College of Psychiatrists (2015)
- Guidelines for Adolescent Depression in Primary Care (2007)

Regulatory Warnings

- In 2004, FDA requested addition of a “black box” warning regarding suicidality in children and adolescents to all antidepressant manufacturer labels

Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis

Andrea Cipriani, Xinyu Zhou*, Cinzia Del Giovane, Sarah E Hetrick, Bin Qin, Craig Whittington, David Coghill, Yuqing Zhang, Philip Hazell, Stefan Leucht, Pim Cuijpers, Juncai Pu, David Cohen, Arun V Ravindran, Yiyun Liu, Kurt D Michael, Lining Yang, Lanxiang Liu, Peng Xie*

Lancet 2016;388:881-90.

Cipriani et al – Background

- **Design:** random-effects network meta-analysis
- **Inclusion criteria:** DB RCTs comparing antidepressants with each other or placebo; children and adolescents; >= 4 week duration; N >= 10 participants
  - Published & unpublished; no language restriction
- **Outcomes:** change in depressive symptoms from baseline to endpoint; proportion of patients discontinuing treatment due to ADRs
- **Funding:** National Basic Research Program of China

Cipriani et al – Results

- Included 31 publications describing 34 RCTs
- Study sample size ranged from 23 to 463 (5260 patients in total)
- Mean age = 13.6 years (SD 2.87)
- Median duration of acute treatment = 8 weeks (range 5-12)

Cipriani et al – Results con'd

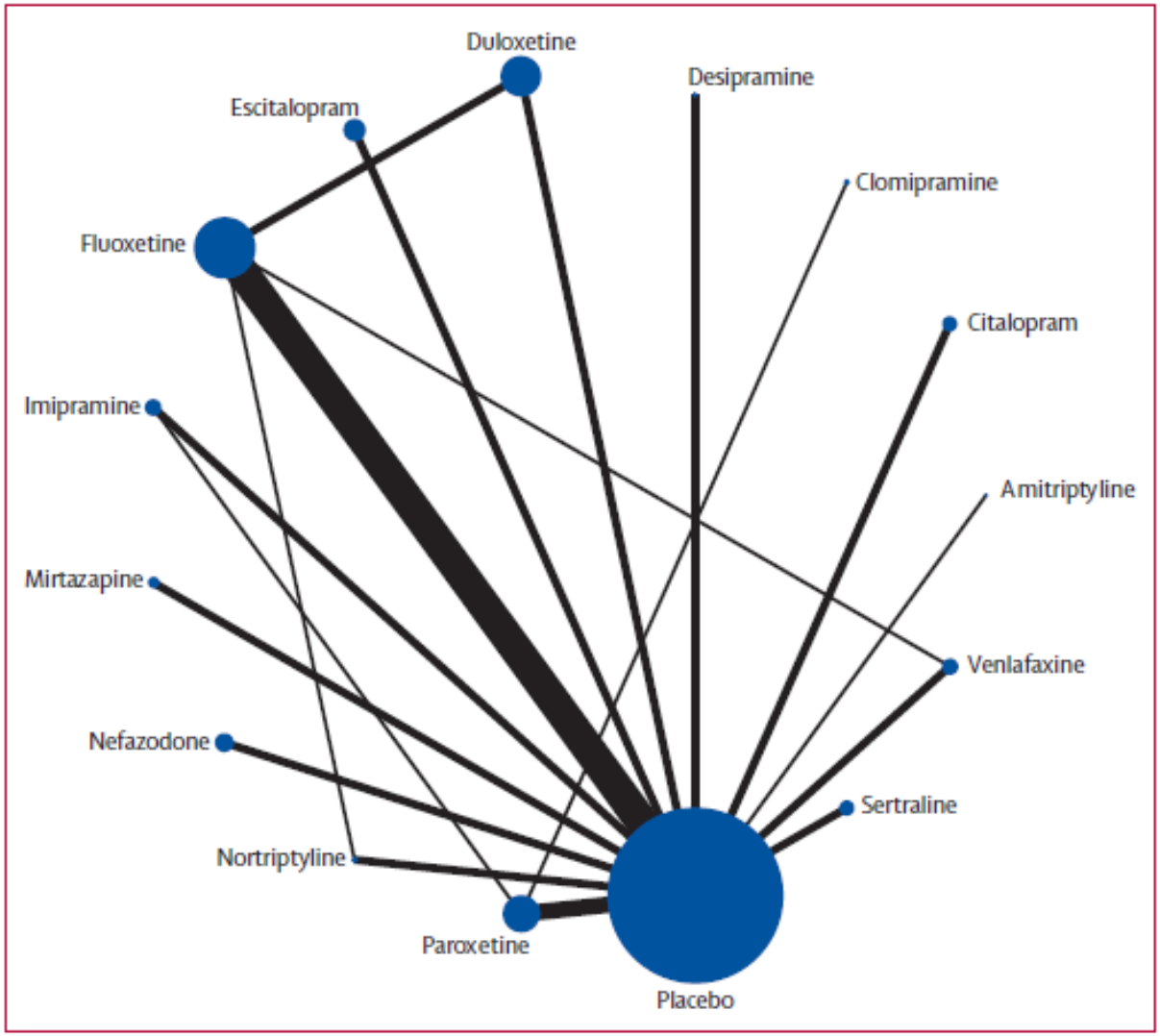


Figure 2: **Network of eligible comparisons for efficacy**
The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size).

Cipriani et al – Results con'd

FLU	0·18 (0·04 to 1·75)	**0·31 (0·13 to 0·95)**	0·39 (0·05 to 1·47)	0·91 (0·09 to 3·49)	0·43 (0·06 to 1·58)	0·69 (0·24 to 3·50)	0·30 (0·07 to 3·06)	0·78 (0·21 to 2·18)	0·96 (0·05 to 4·56)	**0·23 (0·04 to 0·78)**	0·11 (0·03 to 77·0)	1·03 (0·50 to 2·70)	0·43 (0·11 to 3·98)	..
−0·06 (−1·23 to 1·11)	DES	2·05 (0·18 to 8·72)	1·79 (0·11 to 8·70)	4·23 (0·19 to 20·49)	1·96 (0·12 to 9·40)	1·90 (0·47 to 22·04)	3·55 (0·16 to 17·62)	3·61 (0·39 to 14·96)	4·38 (0·11 to 24·29)	1·09 (0·09 to 4·95)	0·32 (0·09 to 377·5)	2·85 (0·83 to 21·80)	1·17 (0·25 to 22·42)	..
−0·16 (−1·05 to 0·72)	−0·10 (−1·49 to1·28)	DUL	1·17 (0·13 to 4·68)	2·73 (0·23 to 11·00)	1·27 (0·14 to 5·05)	1·89 (0·61 to 11·49)	2·27 (0·19 to 9·64)	2·32 (0·53 to 7·26)	2·88 (0·12 to 14·26)	0·68 (0·11 to 2·54)	0·33 (0·09 to 224·8)	**2·80 (1·20 to 9·42)**	1·17 (0·30 to 12·58)	..
−0·25 (−1·13 to 0·64)	−0·19 (−1·54 to 1·17)	−0·09 (−1·28 to 1·10)	VEN	1·17 (0·23 to 18·93)	0·61 (0·14 to 8·69)	2·13 (0·56 to 20·32)	0·92 (0·19 to 16·01)	1·69 (0·47 to 13·33)	0·71 (0·13 to 22·98)	0·40 (0·10 to 4·39)	0·37 (0·10 to 343·2)	**3·19 (1·01 to 18·70)**	1·30 (0·29 to 21·16)	..
−0·27 (−1·39 to 0·84)	−0·21 (−1·68 to 1·26)	−0·11 (−1·46 to 1·23)	−0·02 (−1·33 to 1·28)	MIR	0·93 (0·06 to 4·52)	0·91 (0·23 to 10·97)	0·40 (0·08 to 8·51)	1·71 (0·20 to 7·49)	2·12 (0·05 to 12·37)	0·17 (0·04 to 2·27)	0·18 (0·05 to 151·0)	1·36 (0·41 to 10·99)	0·56 (0·12 to 10·82)	..
−0·28 (−1·38 to 0·82)	−0·22 (−1·68 to 1·24)	−0·12 (−1·46 to 1·21)	−0·03 (−1·34 to 1·27)	−0·01 (−1·43 to 1·40)	SER	1·98 (0·52 to 18·57)	0·85 (0·17 to 15·06)	1·56 (0·44 to 12·09)	0·64 (0·11 to 21·50)	0·37 (0·09 to 4·05)	0·35 (0·09 to 304·7)	2·94 (0·94 to 17·19)	1·20 (0·27 to 18·95)	..
−0·33 (−1·43 to 0·78)	−0·27 (−1·72 to 1·20)	−0·17 (−1·50 to 1·17)	−0·08 (−1·38 to 1·22)	−0·06 (−1·47 to 1·35)	−0·05 (−1·45 to 1·35)	CIT	0·91 (0·07 to 3·89)	0·93 (0·20 to 2·77)	1·17 (0·05 to 5·60)	**0·27 (0·04 to 0·96)**	0·13 (0·03 to 91·24)	1·13 (0·45 to 3·66)	1·18 (0·11 to 4·76)	..
−0·34 (−1·44 to 0·75)	−0·28 (−1·73 to 1·17)	−0·18 (−1·51 to 1·15)	−0·09 (−1·39 to 1·20)	−0·07 (−1·48 to 1·34)	−0·06 (−1·45 to 1·34)	−0·01 (−1·41 to 1·40)	ESC	2·19 (0·22 to 9·23)	2·67 (0·06 to 14·62)	0·63 (0·05 to 2·87)	0·16 (0·05 to 196·9)	1·64 (0·46 to 13·49)	0·68 (0·14 to 13·64)	..
−0·35 (−1·19 to 0·50)	−0·29 (−1·56 to 0·99)	−0·19 (−1·32 to 0·94)	−0·10 (−1·19 to 0·99)	−0·07 (−1·30 to 1·15)	−0·07 (−1·28 to 1·16)	−0·02 (−1·23 to 1·19)	−0·01 (−1·21 to 1·20)	PAR	0·35 (0·07 to 6·80)	**0·22 (0·08 to 0·87)**	0·19 (0·05 to 115·6)	1·59 (0·77 to 3·95)	0·79 (0·26 to 3·77)	..
−0·36 (−1·46 to 0·74)	−0·30 (−1·76 to 1·15)	−0·20 (−1·54 to 1·13)	−0·11 (−1·42 to 1·18)	−0·09 (−1·50 to 1·32)	−0·08 (−1·48 to 1·32)	−0·03 (−1·44 to 1·37)	−0·02 (−1·42 to 1·37)	−0·01 (−1·23 to 1·19)	NEF	0·16 (0·03 to 4·50)	0·11 (0·04 to 241·2)	1·29 (0·30 to 21·89)	0·52 (0·10 to 20·79)	..
−0·49 (−1·57 to 0·58)	−0·44 (−1·88 to 1·01)	−0·33 (−1·65 to 0·98)	−0·25 (−1·53 to 1·03)	−0·22 (−1·61 to 1·17)	−0·22 (−1·60 to 1·17)	−0·17 (−1·55 to 1·22)	−0·16 (−1·54 to 1·22)	−0·15 (−1·21 to 0·91)	−0·13 (−1·52 to 1·26)	IMP	0·67 (0·17 to 471·9)	**5·49 (1·96 to 20·86)**	2·47 (0·62 to 21·47)	..
−0·59 (−2·21 to 1·01)	−0·53 (−2·39 to 1·33)	−0·43 (−2·20 to 1·34)	−0·34 (−2·09 to 1·40)	−0·32 (−2·14 to 1·52)	−0·31 (−2·13 to 1·52)	−0·26 (−2·10 to 1·57)	−0·25 (−2·08 to 1·57)	−0·24 (−1·92 to 1·43)	−0·23 (−2·05 to 1·59)	−0·10 (−1·92 to 1·71)	AMI	0·10 (0·02 to 32·16)	6·38 (0·01 to 24·56)	..
−0·51 (−0·99 to −0·03)	−0·45 (−1·52 to 0·62)	−0·35 (−1·24 to 0·54)	−0·26 (−1·10 to 0·58)	−0·24 (−1·25 to 0·77)	−0·23 (−1·21 to 0·77)	−0·18 (−1·18 to 0·82)	−0·17 (−1·15 to 0·81)	−0·16 (−0·86 to 0·54)	−0·15 (−1·14 to 0·85)	−0·01 (−0·98 to 0·95)	0·08 (−1·45 to 1·61)	PBO	0·79 (0·12 to 2·75)	..
−0·83 (−2·48 to 0·81)	−0·77 (−2·67 to 1·13)	−0·67 (−2·49 to 1·14)	−0·58 (−2·38 to 1·20)	−0·56 (−2·43 to 1·32)	−0·55 (−2·42 to 1·31)	−0·50 (−2·36 to 1·36)	−0·49 (−2·35 to 1·36)	−0·48 (−1·90 to 0·93)	−0·47 (−2·33 to 1·39)	−0·34 (−2·10 to 1·43)	−0·24 (−2·43 to 1·95)	−0·32 (−1·90 to 1·25)	CLO	..
−1·65 (−2·57 to −0·72)	**−1·59 (−2·98 to −0·21)**	**−1·49 (−2·71 to −0·27)**	**−1·40 (−2·60 to −0·20)**	**−1·38 (−2·71 to −0·04)**	**−1·37 (−2·70 to −0·05)**	−1·32 (−2·65 to 0·01)	−1·31 (−2·63 to 0·01)	**−1·30 (−2·43 to −0·18)**	−1·29 (−2·61 to 0·04)	−1·15 (−2·46 to 0·15)	−1·06 (−2·81 to 0·71)	**−1·14 (−2·02 to −0·25)**	−0·82 (−2·61 to 0·99)	NOR

Treatment | Efficacy (mean overall change in symptoms, SMD [95% CrI]) | Tolerability (discontinuation due to adverse events, OR [95% CrI])

Figure 3. Network meta-analysis of efficacy and tolerability

Cipriani et al – Results con'd

- Efficacy
  - Fluoxetine > placebo (-0.51; -0.99 to -0.03)
- Tolerability
  - Fluoxetine > duloxetine, imipramine
  - Placebo > duloxetine, venlafaxine, imipramine

Cipriani et al – Conclusions

- Fluoxetine *may* reduce depressive symptoms in children and adolescents with MDD
  - Clinical significance of this is uncertain
  - Can be considered for patients who do not have access to psychotherapy or who have not responded to non-pharmacological treatments
- Other available antidepressants do not appear to have benefits and are not recommended

Cipriani et al – Strengths & Limitations

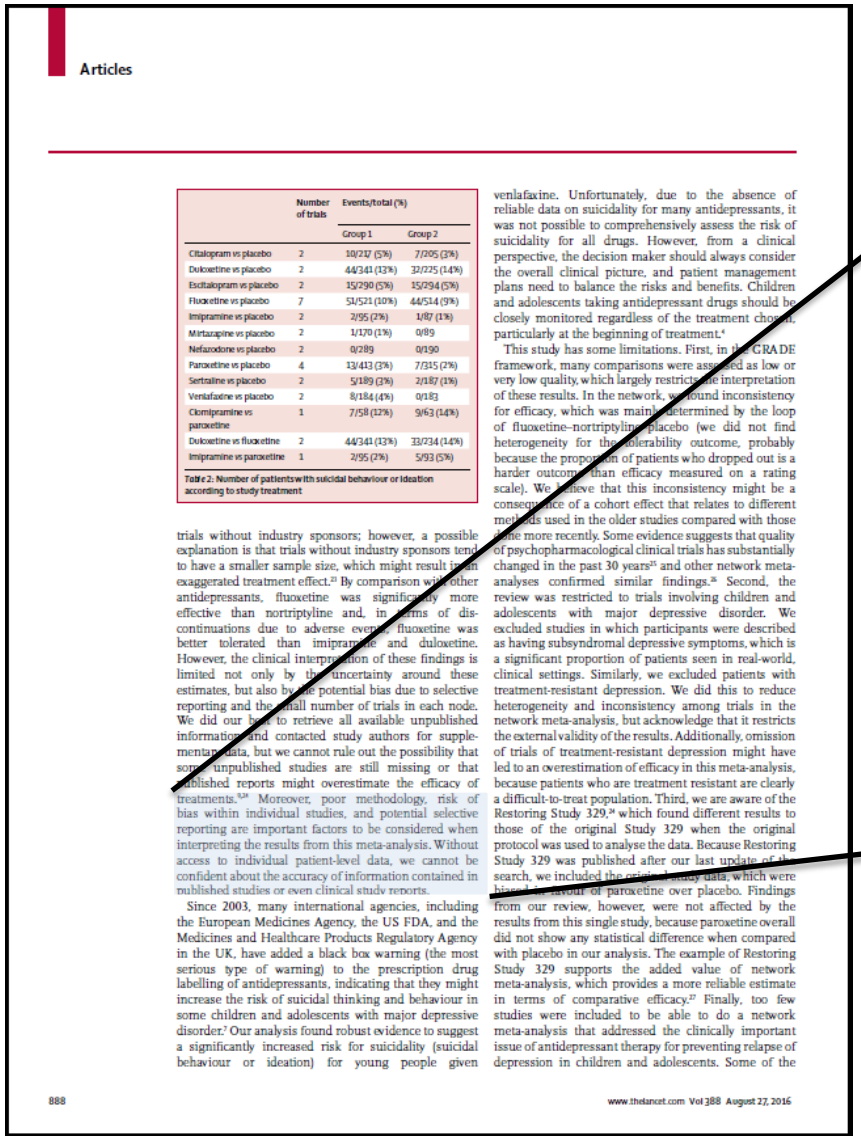
- Strengths
  - Comprehensive retrieval and analysis of available literature
- Limitations
  - Many comparisons were of “low” or “very low” quality (GRADE system)
  - Excluded trials of patients with subsyndromal depressive symptoms or treatment resistant depression
  - Individual patient-level data unavailable

Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

Joanna Le Noury,[1] John M Nardo,[2] David Healy,[1] Jon Jureidini,[3] Melissa Raven,[3] Catalin Tufanaru,[4] Elia Abi-Jaoude[5]

BMJ 2015;351:h4320

Cipriani et al – Conclusions



Articles

	Number of trials	Events/total (%)	
		Group 1	Group 2
Citalopram vs placebo	2	10/217 (5%)	7/205 (3%)
Duloxetine vs placebo	2	44/341 (13%)	32/225 (14%)
Escitalopram vs placebo	2	15/290 (5%)	15/294 (5%)
Fluoxetine vs placebo	7	51/521 (10%)	44/514 (9%)
Imipramine vs placebo	2	2/95 (2%)	1/87 (1%)
Mirtazapine vs placebo	2	1/170 (1%)	0/89
Nefazodone vs placebo	2	0/289	0/190
Paroxetine vs placebo	4	13/413 (3%)	7/315 (2%)
Sertraline vs placebo	2	5/189 (3%)	2/187 (1%)
Venlafaxine vs placebo	2	8/184 (4%)	0/183
Clomipramine vs paroxetine	1	7/58 (12%)	9/63 (14%)
Duloxetine vs fluoxetine	2	44/341 (13%)	33/234 (14%)
Imipramine vs paroxetine	1	2/95 (2%)	5/93 (5%)

Table 2: Number of patients with suicidal behaviour or ideation according to study treatment

trials without industry sponsors; however, a possible explanation is that trials without industry sponsors tend to have a smaller sample size, which might result in an exaggerated treatment effect.[25] By comparison with other antidepressants, fluoxetine was significantly more effective than nortriptyline and, in terms of discontinuations due to adverse events, fluoxetine was better tolerated than imipramine and duloxetine. However, the clinical interpretation of these findings is limited not only by the uncertainty around these estimates, but also by the potential bias due to selective reporting and the small number of trials in each node. We did our best to retrieve all available unpublished information and contacted study authors for supplementary data, but we cannot rule out the possibility that some unpublished studies are still missing or that published reports might overestimate the efficacy of treatments.[9,26] Moreover, poor methodology, risk of bias within individual studies, and potential selective reporting are important factors to be considered when interpreting the results from this meta-analysis. Without access to individual patient-level data, we cannot be confident about the accuracy of information contained in published studies or even clinical study reports.

Since 2003, many international agencies, including the European Medicines Agency, the US FDA, and the Medicines and Healthcare Products Regulatory Agency in the UK, have added a black box warning (the most serious type of warning) to the prescription drug labelling of antidepressants, indicating that they might increase the risk of suicidal thinking and behaviour in some children and adolescents with major depressive disorder.[7] Our analysis found robust evidence to suggest a significantly increased risk for suicidality (suicidal behaviour or ideation) for young people given venlafaxine. Unfortunately, due to the absence of reliable data on suicidality for many antidepressants, it was not possible to comprehensively assess the risk of suicidality for all drugs. However, from a clinical perspective, the decision maker should always consider the overall clinical picture, and patient management plans need to balance the risks and benefits. Children and adolescents taking antidepressant drugs should be closely monitored regardless of the treatment chosen, particularly at the beginning of treatment.[4]

This study has some limitations. First, in the GRADE framework, many comparisons were assessed as low or very low quality, which largely restricts the interpretation of these results. In the network, we found inconsistency for efficacy, which was mainly determined by the loop of fluoxetine–nortriptyline–placebo (we did not find heterogeneity for the tolerability outcome, probably because the proportion of patients who dropped out is a harder outcome than efficacy measured on a rating scale). We believe that this inconsistency might be a consequence of a cohort effect that relates to different methods used in the older studies compared with those done more recently. Some evidence suggests that quality of psychopharmacological clinical trials has substantially changed in the past 30 years[25] and other network meta-analyses confirmed similar findings.[26] Second, the review was restricted to trials involving children and adolescents with major depressive disorder. We excluded studies in which participants were described as having subsyndromal depressive symptoms, which is a significant proportion of patients seen in real-world, clinical settings. Similarly, we excluded patients with treatment-resistant depression. We did this to reduce heterogeneity and inconsistency among trials in the network meta-analysis, but acknowledge that it restricts the external validity of the results. Additionally, omission of trials of treatment-resistant depression might have led to an overestimation of efficacy in this meta-analysis, because patients who are treatment resistant are clearly a difficult-to-treat population. Third, we are aware of the Restoring Study 329,[24] which found different results to those of the original Study 329 when the original protocol was used to analyse the data. Because Restoring Study 329 was published after our last update of the search, we included the original study data, which were biased in favour of paroxetine over placebo. Findings from our review, however, were not affected by the results from this single study, because paroxetine overall did not show any statistical difference when compared with placebo in our analysis. The example of Restoring Study 329 supports the added value of network meta-analysis, which provides a more reliable estimate in terms of comparative efficacy.[27] Finally, too few studies were included to be able to do a network meta-analysis that addressed the clinically important issue of antidepressant therapy for preventing relapse of depression in children and adolescents. Some of the

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... poor methodology, risk of bias within individual studies, and potential selective reporting are important factors to be considered when interpreting the results from this meta-analysis. Without access to individual patient-level data, we cannot be confident about the accuracy of information contained in published studies or even clinical study reports.

Summary and Conclusions

- Based on available data, fluoxetine is only antidepressant that may have benefit in children and adolescents
- Benefits may be overstated and harms may be understated for antidepressant use in this patient population – important to be aware of limitations of published literature

THANK YOU

References

- **Cipriani A, Zhou X, Del Giovane C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet 2016;388:881-90*.**
- Costello EJ, Erkanli A, Angold A. Is there an epidemic of child or adolescent depression? *J Child Psychol Psychiatry 2006;47:1263-71.*
- Hopkins K, Crosland P, Elliott N, Bewley S, for the Clinical Guidelines Update Committee B. Diagnosis and management of depression in children and young people: summary of updated NICE guidance. *BMJ 2015;350:h824*.
- Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry 2015;49:1087–206.*
- AACAP Practice Parameter for the Assessment and Treatment of Children and Adolescents With Depressive Disorders. *J Am Acad Child Adolesc Psychiatry 2007;46:1503-26*.
- US Food and Drug Administration. Labeling Change Request Letter for Antidepressant Medications. Oct 15, 2004. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096352.htm
- Le Noury J, Nardo JM, Healy D, et al. Restoring Study 329: Efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ 2015;351:h4320*.

Recommended Reading

- Jureidini JN, Amsterdam JD, McHenry LB. The citalopram CIT-MD-18 pediatric depression trial: Deconstruction of medical ghostwriting, data mischaracterisation and academic malfesance. *Int J Risk Saf Med 2016;28:33-43*.
- Ebrahim S, Bance S, Athale A, et al. Meta-analyses with industry involvement are massively published and report no caveats for antidepressants. *J Clin Epi 2016;70:155-63*.
- Sharma T, Guski LS, Freund N, Gotzsche PC. Suicidality and aggression during antidepressant treatment: Systematic review and meta-analyses based on clinical study reports. *BMJ 2016;352:i65*.
- Hughes S, Cohen D, Jaggi R. Differences in reporting serious adverse events in industry sponsored clinical trial registries and journal articles on antidepressant and antipsychotic drugs: a crosssectional study. *BMJ Open 2014;4:e005535*.