

En genomgång av vetenskapligt underlag för antidepressiv medicin

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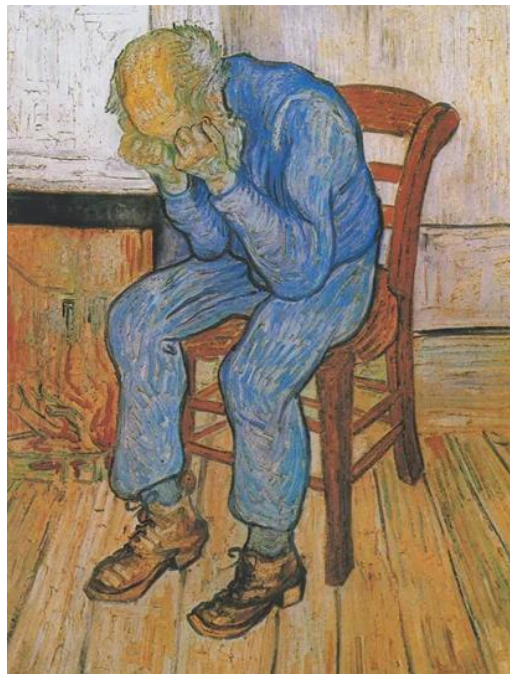
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Jäv: skrivit en bok om antidepressiva läkemedel



Vilka har träffat nedstämda och ångestfyllda patienter som beskriver dramatiskt positiva effekter av antidepressiva?



Några begrepp

open science och rådata

statistisk signifikans

klinisk signifikans

cohen's d

genomsnittlig poängskillnad

respons/remission

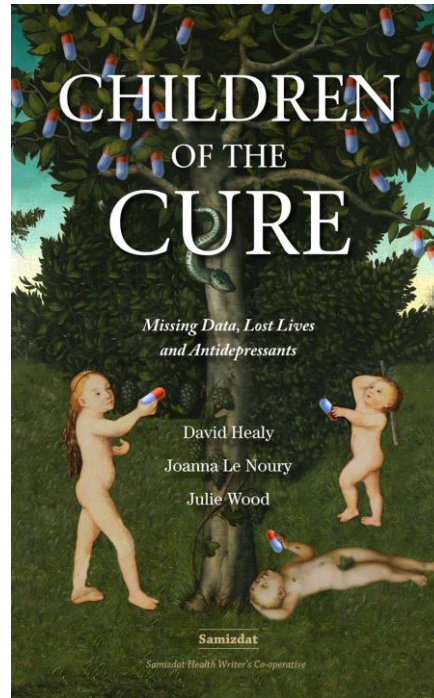
NNT/NNH

efficacystudie

effectivenesstudie

Studie 329 - världens mest kända läkemedelsstudie

“Paroxetin tolereras generellt väl och är effektivt vid depression hos ungdomar.”



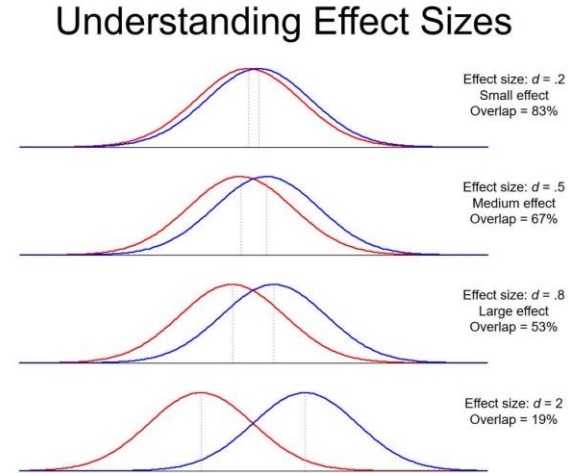
Keller et al (2001). Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, 40(7), 762–772

Healy, D. (2012). *Pharmageddon*. University of California Press.

Le Noury et al (2015). Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ*, 351.

Cohen's d och HAM-D

cohen's d = a value measuring the strength of the relationship between two variables in a population, or a sample-based estimate of that quantity.

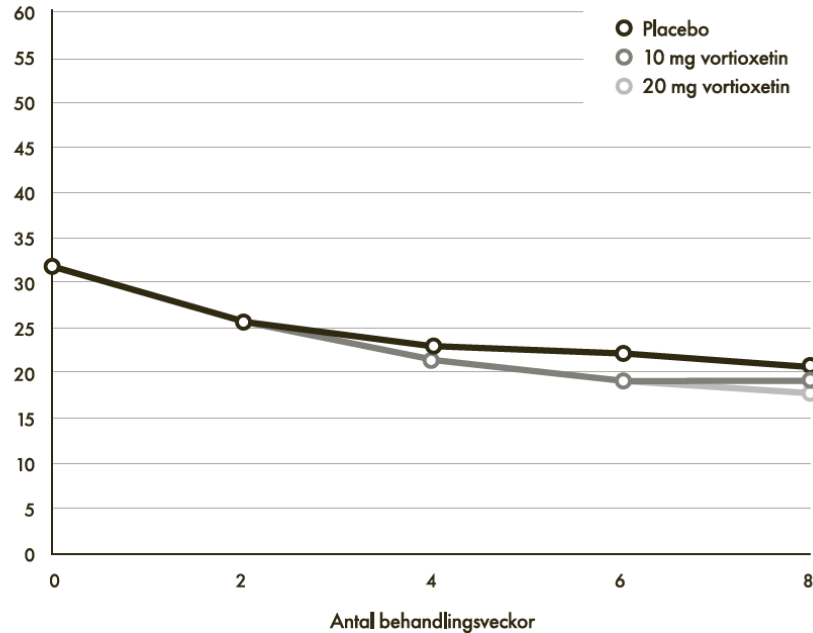


Moncrieff, J., & Kirsch, I. (2015). Empirically derived criteria cast doubt on the clinical significance of antidepressant-placebo differences. *Contemporary Clinical Trials*, 43, 60-62.

Vad visar systematiska översikter över efficacystudier?

Skillnad i effekt mellan behandling med vortioxetin och placebo vid depression

MADRS-skalan



Jacobsen, P. et al (2015). A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. *The Journal of clinical psychiatry*, 76(5), 16740.

Några uppmärksammade meta-analyser

Cipriani et al: 474 studier - 21 olika antidepressiva läkemedel

Jakobsen et al: 131 studier. - SSRI

Cipriani et al (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *The Lancet*, 391(10128), 1357–1366.

Jakobsen et al (2017). Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. *BMC Psychiatry*, 17(1), 1–28.

Vad visade studierna?

Cipriani:

- genomsnittlig baseline HAM-D: 25.7 poäng
- 1,97 poängs genomsnittlig poängskillnad
- effektstorlek: 0,30

Jakobsen:

- effektstorlek: $<0,30$
- ≤ 23 HAM-D: 1,29 poäng på HAM-D
- >23 HAM-D: 2,69 poäng på HAM-D

Hieronymus sub item-analyser på HAM-D

- I DEPRESSED MOOD** (*sadness, hopeless, helpless, worthless*)
- 0 Absent.
 - 1 These feeling states indicated only on questioning.
 - 2 These feeling states spontaneously reported verbally.
 - 3 Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.
 - 4 Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

“...används data från 32 RCT:er på SSRI-preparat och visade en sammanvägd effektstorlek (SMD) för nedstämdhet på 0,4...”

Hieronymus et al (2016). Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression. *Molecular psychiatry*, 21(4), 523-530.

Fluoxetin vid depression hos barn

“Den forskning som gjorts på användning av selektiva serotoninåterupptagshämmare (SSRI) vid depression hos barn är en historia som bygger på förvirring, manipulation och institutionellt misslyckande.”

Källa?

Genomgång av samtliga studier på depression för barn 1990-2005

- 35 studier, 10.000 deltagare
- studieresultat jämfördes med kliniska studierapporter
- endast en visade statistiskt signifikant skillnad

Healy, D., Le Noury, J., & Jureidini, J. (2019). Paediatric antidepressants: benefits and risks. *International Journal of Risk & Safety in Medicine*, 30(1), 1–7.

Gøtzsche, P. C., & Healy, D. (2022). Restoring the two pivotal fluoxetine trials in children and adolescents with depression. *International Journal of Risk & Safety in Medicine*, (Preprint), 1–24.

Bias i efficacy-studierna

Jakobsen et al: samtliga 131 studier bedömdes lida av hög risk för bias till följd av en rad olika metodfel.

Cipriani et al: bedömde 18% av de inkluderade studierna led av låg risk för bias, 73% som “moderat” och 9% som hög risk för bias.

Bruten blindning



Rabkin, J. G., Markowitz, J. S., Stewart, J., McGrath, P., Harrison, W., Quitkin, F. M., & Klein, D. F. (1986). How blind is blind? Assessment of patient and doctor medication guesses in a placebo-controlled trial of imipramine and phenelzine. *Psychiatry Research*, 19(1), 75–86.

Margraf, J., Ehlers, A., Roth, W. T., Clark, D. B., Sheikh, J., Agras, W. S., & Taylor, C. B. (1991). How »blind« are double-blind studies?. *Journal of Consulting and Clinical Psychology*, 59(1), 184.

Konsekvenserna av oklar blindning för utfallen

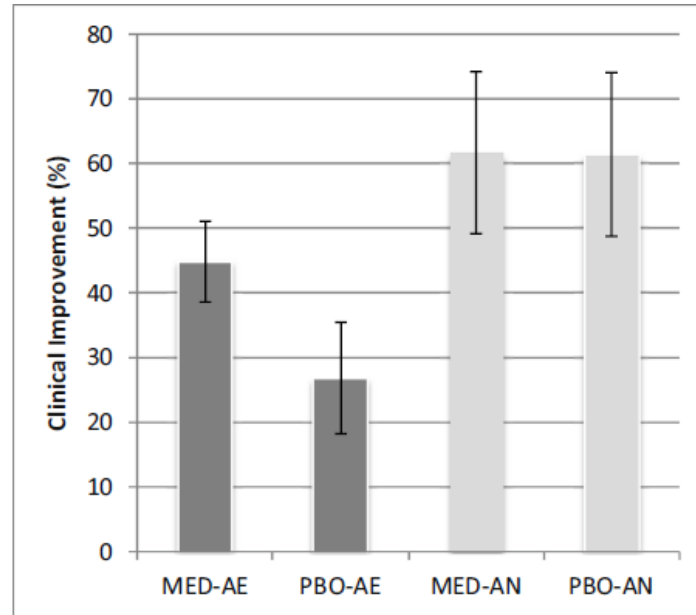
En genomgång visade att bias i form av frånvaro av, eller oklar, dubbelblindning medförde att effekterna överskattades med i genomsnitt 13 procent, och att de överskattades mest i studier med subjektiva utfallsmått – som vid utvärdering av antidepressiva.

Savović, J., Jones, H. E., Altman, D. G., Harris, R. J., Jüni, P., Pildal, J., ... & Sterne, J. A. C. (2012). Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. *Health Technology Assessment*, 16(35), 1–82.

Varför bryts blindningen?



Resultat i subgrupperna tidigare AD-användare vs AD-naiva



Hunter, A. M., Cook, I. A., & Leuchter, A. F. (2010). Impact of antidepressant treatment history on clinical outcomes in placebo and medication treatment of major depression. *Journal of clinical psychopharmacology*, 30(6), 748-751.

Hunter, A. M., Cook, I. A., Tartter, M., Sharma, S. K., Disse, G. D., & Leuchter, A. F. (2015). Antidepressant treatment history and drug-placebo separation in a placebo-controlled trial in major depressive disorder. *Psychopharmacology*, 232, 3833-3840.

Vem skattar förbättringen i studierna?

Behandlingsresultat i studier utvärderas av kliniker.

Kliniker överskattar effekterna av behandling.

Hengartner, M. P., & Plöderl, M. (2018). Statistically significant antidepressant-placebo differences on subjective symptom-rating scales do not prove that the drugs work: *Frontiers in Psychiatry*, 9, 517.

Vems opplevelse av effekten ska vi gå på?

Table 1
Influence of Type of Outcome Measure on Effect Sizes for Standard and Newer Antidepressants

Type of drug and rating source	N of drug-placebo studies	Mean effect size (d)	Combined Z	p	Fail-safe N
Standard antidepressant					
Clinician	22	.25	4.49	<.000003	153
Patient	11	.06	1.09	ns	—
Newer antidepressant					
Clinician	22	.31	5.17	<.0000003	195
Patient	11	.12	1.79	<.04	2

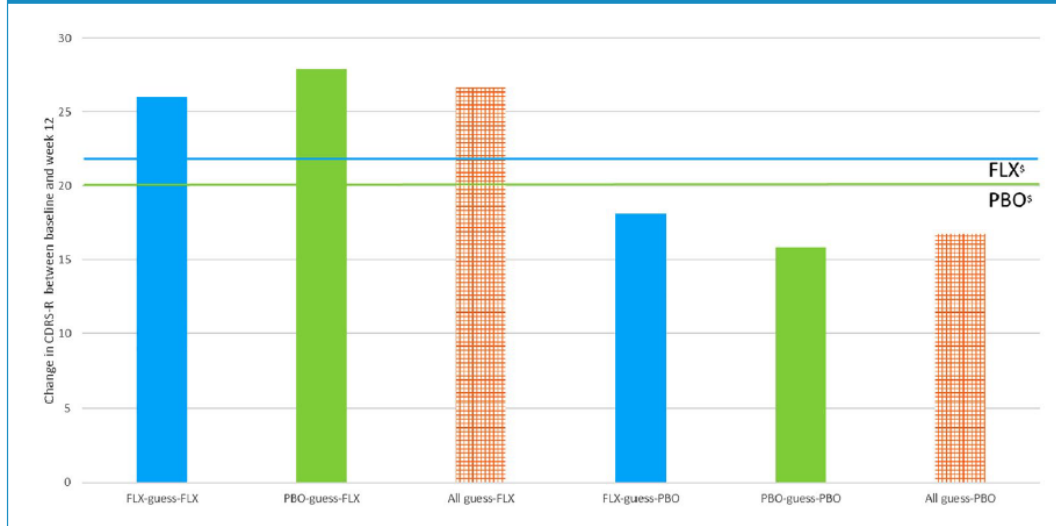
Greenberg, R. P., Bornstein, R. F., Greenberg, M. D., & Fisher, S. (1992). A meta-analysis of antidepressant outcome under »blinder« conditions. *Journal of Consulting and Clinical Psychology*, 60(5), 664.

Spielmanns, G. I., & Gerwig, K. (2014). The efficacy of antidepressants on overall well-being and self-reported depression symptom severity in youth: a meta-analysis. *Psychotherapy and Psychosomatics*, 83(3), 158–164.

Göttsche, P. C., & Healy, D. (2022). Restoring the two pivotal fluoxetine trials in children and adolescents with depression. *International Journal of Risk & Safety in Medicine*, (Preprint), 1–24.

TADS-studien: utfall utifrån vad patienterna tror att de fått

Figure 2. Change from baseline to week 12 in CDRS-R according to adolescents' guesses about treatment allocation at week 6.

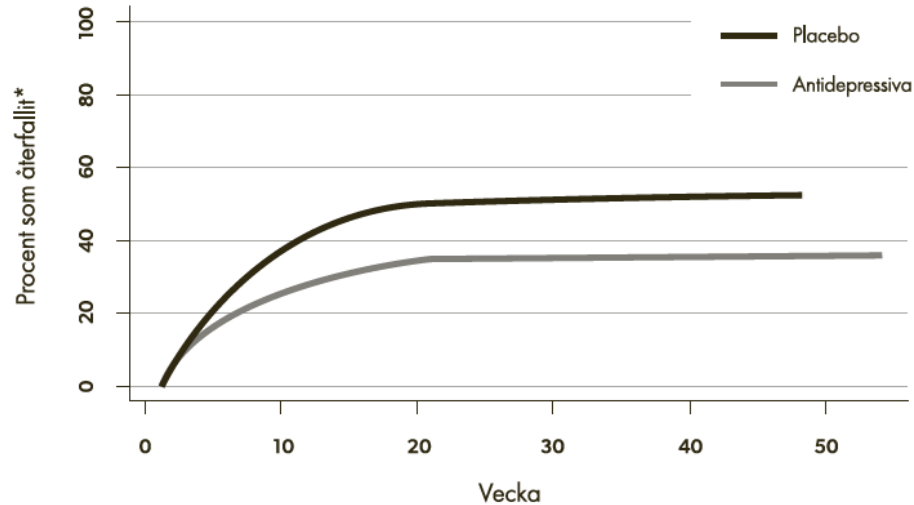


[§]The upper line represents the mean change in CDRS-R for adolescents allocated to FLX and the lower line represents the change in CDRS-R for adolescents allocated to PBO.

Jureidini, J., Moncrieff, J., Klau, J., Aboustate, N., & Raven, M. (2024). Treatment guesses in the Treatment for Adolescents with Depression Study: Accuracy, unblinding and influence on outcomes. *Australian & New Zealand Journal of Psychiatry*, 58(4), 355-364.

Högberg, G., Antonuccio, D. O., & Healy, D. (2015). Suicidal risk from TADS study was higher than it first appeared. *International Journal of Risk & Safety in Medicine*, 27(2), 85-91.

Randomiserade utsättningsstudier



* I relation till dem som är kvar i studien.

Skillnaden i återfall veckorna efter att patienterna som stått på antidepressiva slumpats till att antingen fortsätta med antidepressiva eller gå över till placebo. Bilden är en förenklad illustration av förloppet.

Hur går det för patienterna i effectivenessstudierna?



STAR*D

Hur går det för patienterna över tid?



- Hengartner, M. P., Angst, J., & Rössler, W. (2018). Antidepressant use prospectively relates to a poorer long-term outcome of depression: results from a prospective community cohort study over 30 years. *Psychotherapy and Psychosomatics*, 87(3), 181–183.
- Vittengl, J. R. (2017). Poorer long-term outcomes among persons with major depressive disorder treated with medication. *Psychotherapy and Psychosomatics*, 86(5), 302–304.
- Ronalds, C., Creed, F., Stone, K., Webb, S., & Tomenson, B. (1997). Outcome of anxiety and depressive disorders in primary care. *The British Journal of Psychiatry*, 171(5), 427–433.

Är mer läkemedel alltid bättre?



Frye et al (2000). The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. *Journal of Clinical Psychiatry*, 61(1), 9–15.

Rittmannsberger, H. (2002). The use of drug monotherapy in psychiatric inpatient treatment. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 26(3), 547–551.

Stassen, et al . (2022). Detailing the effects of polypharmacy in psychiatry: longitudinal study of 320 patients hospitalized for depression or schizophrenia. *European archives of psychiatry and clinical neuroscience*, 1-17.

Hur ser det ut när man använder mer relevanta utfallsmått?



Hengartner, M. P., Passalacqua, S., Andreae, A., Heinsius, T., Hepp, U., Rössler, W., & Von Wyl, A. (2019). Antidepressant use during acute inpatient care is associated with an increased risk of psychiatric rehospitalisation over a 12-month follow-up after discharge. *Frontiers in psychiatry*, 10, 79.

Suicidhändelser

Kom ihåg att ha CDR-förfarande i bakhuvudet

Behandling	Antal patienter	Antal självmord	Antal självmordsförsök	Självmord och självmordsförsök i procent
Sertralin	2 053	2	7	0,44
Jämförelseläkemedel	595	0	1	0,17
Placebo	786	0	2	0,25
Washout		0	3	
Paroxetin	2 963	5	40	1,52
Jämförelseläkemedel	1 151	3	12	1,30
Placebo	554	0	3	0,54
Washout		2	2	
Nefazodon	3 496	9	12	0,60
Jämförelseläkemedel	958	0	6	0,63
Placebo	875	0	1	0,11
Mirtazapin	2 425	8	29	1,53
Jämförelseläkemedel	977	2	5	0,72
Placebo	494	0	3	0,61
Bupropion	1 942	3	–	
Placebo	370	0	–	
Citalopram	4 168	8	91	2,38
Placebo	691	1	10	1,59
Fluoxetin	1 427	1	12	0,91
Placebo	370	0	0	0
Washout		1	0	
Venlafaxin	3 082	7	36	1,40
Placebo	739	1	2	0,41
Alla undersökta läkemedel	21 556	43	232	1,28
Alla SSRI-läkemedel	13 693	23	186	1,53
Jämförelseläkemedel	3 681	5	24	0,79
Total Placebo	4 879	2	21	0,47
Placebo i SSRI-studier	3 140	2	16	0,57

Healy, D., & Whitaker, C. (2003). Antidepressants and suicide: risk–benefit conundrums. *Journal of Psychiatry and Neuroscience*, 28(5), 331-337.

Teicher, M. H., Glod, C., & Cole, J. O. (1990). Emergence of intense suicidal preoccupation during

Zainal, N. H. (2023). Is combined antidepressant medication (ADM) and psychotherapy better than either monotherapy at preventing suicide attempts and other psychiatric serious adverse events for depressed patients? A rare events meta-analysis. *Psychological Medicine*, 1–16.

fluoxetine treatment. *The American Journal of Psychiatry*, 147(2), 207–210.

Varför tycks det gå sämre på gruppnivå om patienter får AD?

Iatrogena effekter och förskrivningskaskader:

Psykologiska effekter

Fava, G. A. (1999). Potential sensitising effects of antidepressant drugs on depression. *CNS drugs*, 12(4), 247-256.

Fava, G. A., & Offidani, E. (2011). The mechanisms of tolerance in antidepressant action. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 35(7), 1593-1602.

Deacon et al (2009). The chemical imbalance explanation of depression: Reducing blame at what cost? *Journal of Social and Clinical Psychology*, 28(4), 415-435.

Wilens et al. (2003). A systematic chart review of the nature of psychiatric adverse events in children and adolescents treated with selective serotonin reuptake inhibitors. *Journal of Child and Adolescent Psychopharmacology*, 13(2), 143-152.

Hur bör vi använda AD i vården?



Efficacy- och effektivitetsstudier

Singal (2014). A Primer on Effectiveness and Efficacy Trials.

Sheldon (2015) How Commonly Used Inclusion and Exclusion Criteria in Antidepressant Registration Trials Affect Study Enrollment

Zimmerman (2002) Are Subjects in Pharmacological Treatment Trials of Depression Representative of Patients in Routine Clinical Practice?

Cohen's d och genomsnittlig poängskillnad på HAM-D

National Institute for Clinical Excellence. Depression: management of depression in primary and secondary care. Clinical practice guideline No 23. London: NICE, 2004

Hengartner, M. P., & Plöderl, M. (2022). Estimates of the minimal important difference to evaluate the clinical significance of antidepressants in the acute treatment of moderate-to-severe depression. *BMJ Evidence-Based Medicine*, 27(2), 69-73.

Leucht, S. (2013). What does the HAMD mean?. *Journal of affective disorders*, 148(2-3), 243-248.

Moncrieff, J. (2015). Empirically derived criteria cast doubt on the clinical significance of antidepressant-placebo differences. *Contemporary Clinical Trials*, 43, 60-62.

Referenser STAR*D

- Rush, et al (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. *American Journal of Psychiatry*, 163(11), 1905–1917
- Rush et al (2009). STAR* D: revising conventional wisdom. *CNS drugs*, 23, 627-647.
- Pigott, H. E. (2011). STAR* D: A tale and trail of bias. *Ethical Human Psychology and Psychiatry*, 13(1), 6-28.
- Pigott, H. E. (2015). The STAR* D trial: It is time to reexamine the clinical beliefs that guide the treatment of major depression. *The Canadian Journal of Psychiatry*, 60(1), 9–13.
- Pigott et al (2010). Efficacy and effectiveness of antidepressants: current status of research. *Psychotherapy and psychosomatics*, 79(5), 267-279.
- Kirsch et al(2018). Do outcomes of clinical trials resemble those of »real world« patients? A reanalysis of the STAR* D antidepressant data set. *Psychology of Consciousness: Theory, Research, and Practice*, 5(4), 339.
- Pigott et al (2023). What are the treatment remission, response and extent of improvement rates after up to four trials of antidepressant therapies in real-world depressed patients? A reanalysis of the STAR* D study's patient-level data with fidelity to the original research protocol. *BMJ open*, 13(7), e063095.
- Pigott et al(2024). Open Letter to call for the retraction of the five STAR*D articles published in the *American Journal of Psychiatry* (AJP)
<https://www.madinamerica.com/2024/10/investigators-who-blew-the-whistle-on-stard-fraud-call-for-retraction-of-five-ajp-articles/>
- Gibbons et al (2012). Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo- controlled randomized trials of fluoxetine and venlafaxine. *Archives of general psychiatry*, 69(6), 572–579.
- Whiteford et al (2013). Estimating remission from untreated major depression: a systematic review and meta-analysis. *Psychological medicine*, 43(8), 1569–1585.