Antidepressiva zweiter Wahl

Datenlage zu Switch, Augmentation und Kombination

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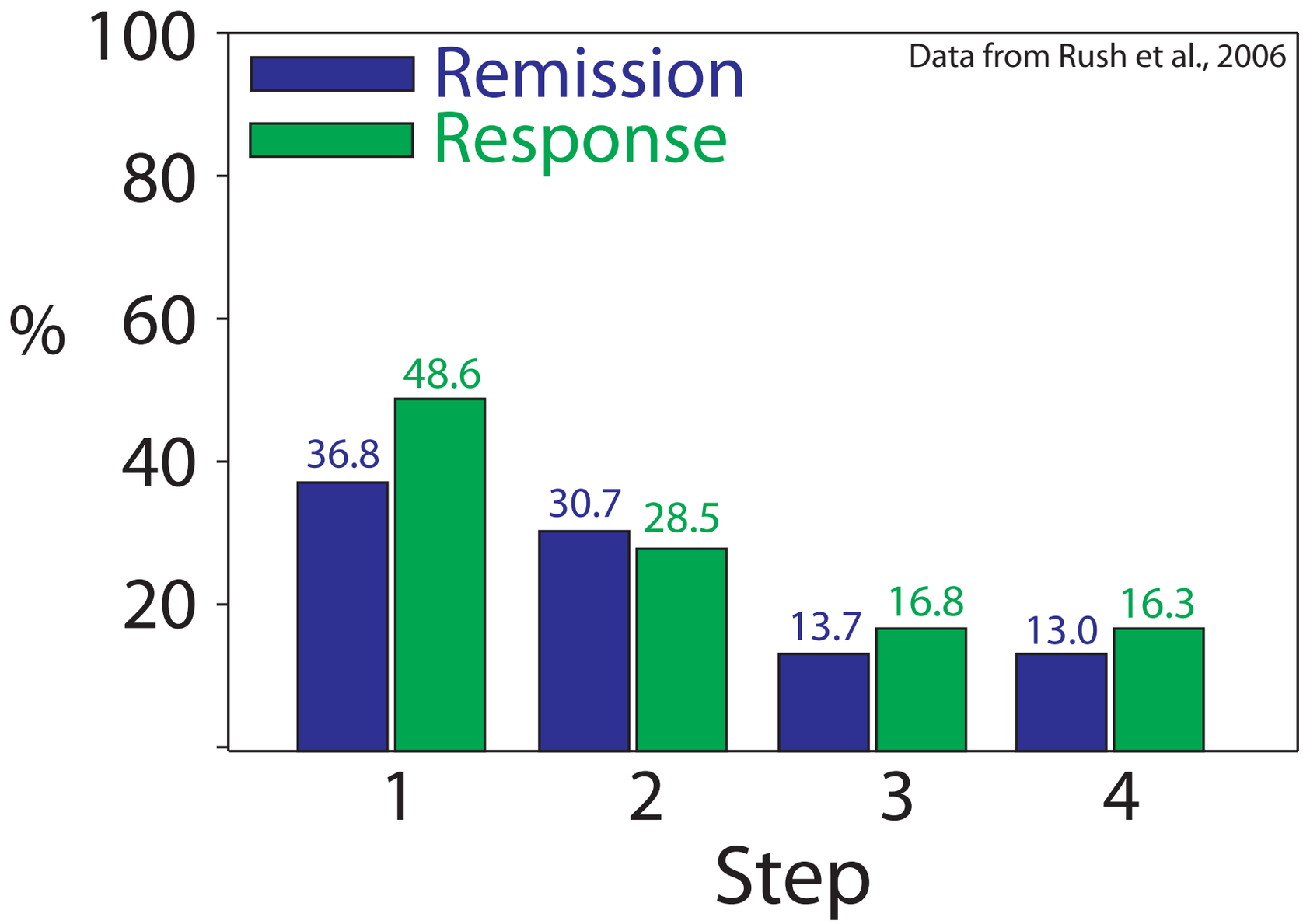
Klappt's?


Data from Rush et al., 2006
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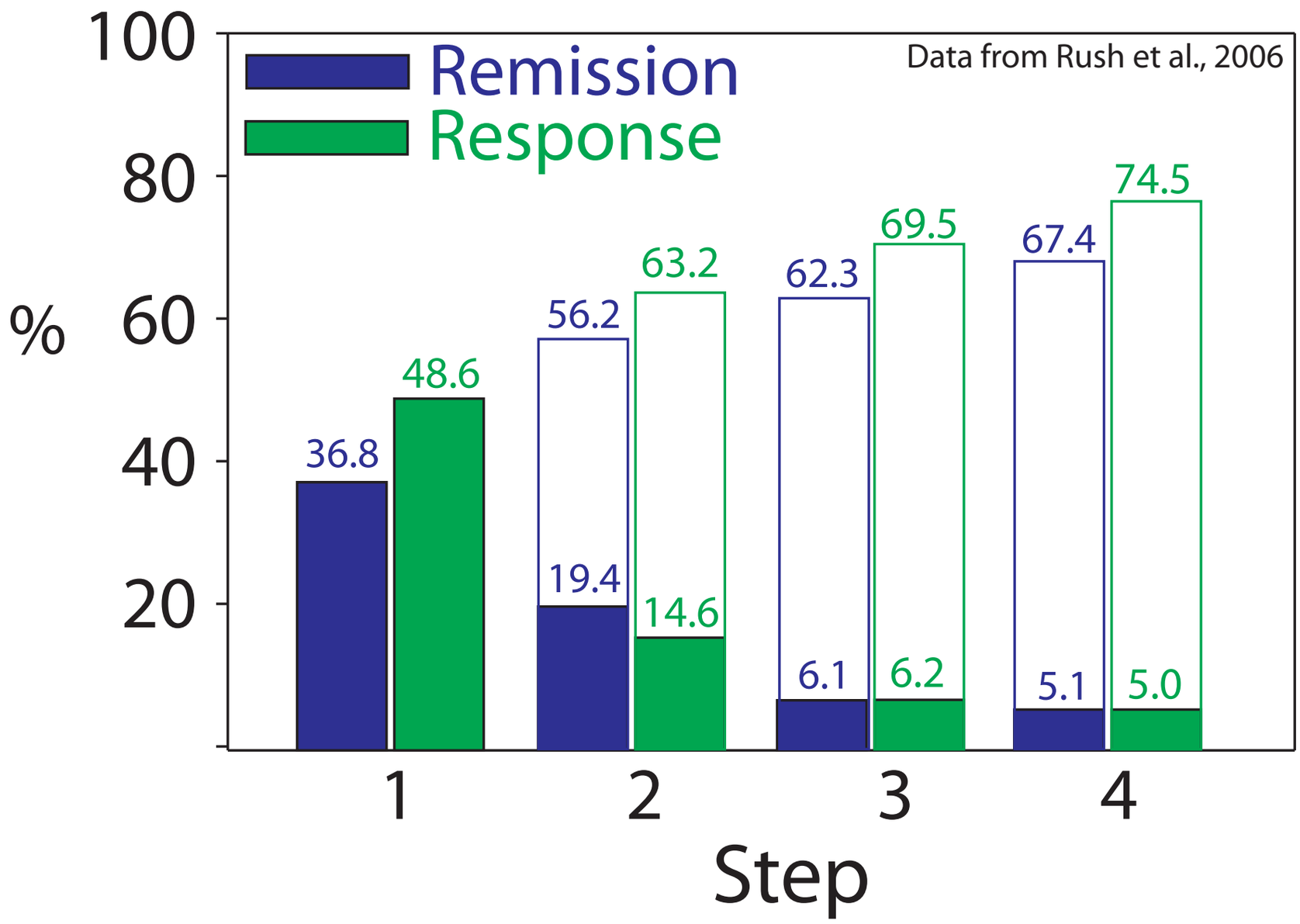
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Step

Strategien

- Switch
  - zu anderem SSRI/SNRI
  - zu Mirtazapin
- Augmentation
  - Lithium
  - Atypikum
- Kombination
  - Mirtazapin/Mianserin + SSRI/SNRI
  - Desipramine + SSRI/SNRI

Switch SSRI -> Venlafaxin

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- Vergleichbar viele Daten

Switch SSRI -> Venlafaxin

- Vergleichbar viele Daten
- 2 DB-RCTs.
  - Venlafaxin: 37% vs Paroxetin 18%
    - *Poirier & Boyer 1999, BJP. n=122. 2x failures*
  - Venlafaxin = Citalopram XR.
    - *Lenox-Smith & Jian 2008, ICPsychoph. n=406. 1x failure*
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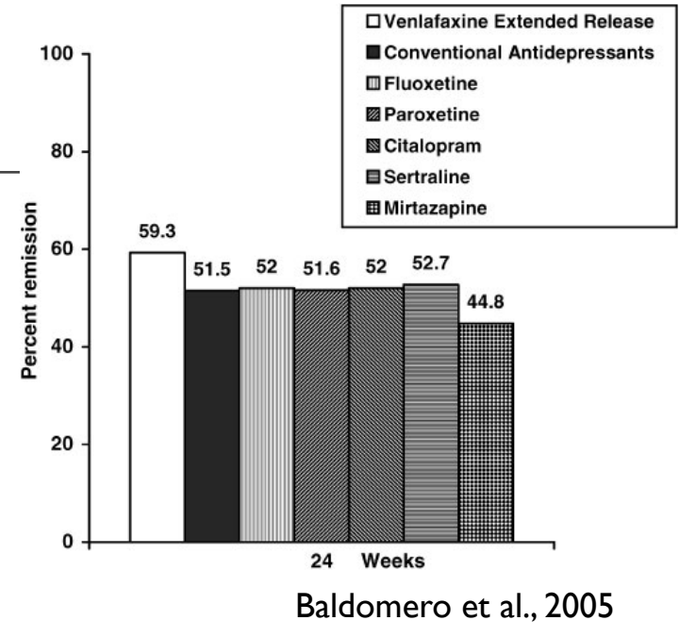
- Unblinded
  - STAR*D (n=727) Venlafaxin = Sertralin = Bupropion
  - ARGOS (n=3097) Venlafaxin 59.3% vs SSRI 51.5%

Switch SSRI -> Venlafaxin



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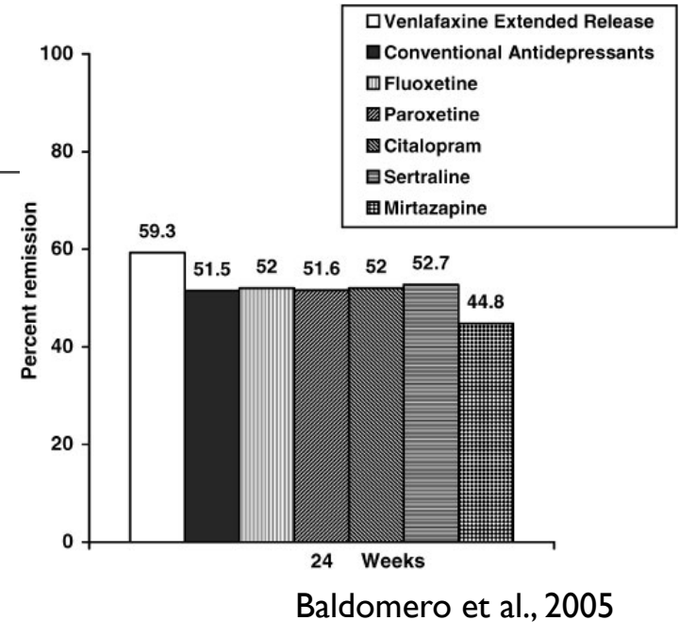

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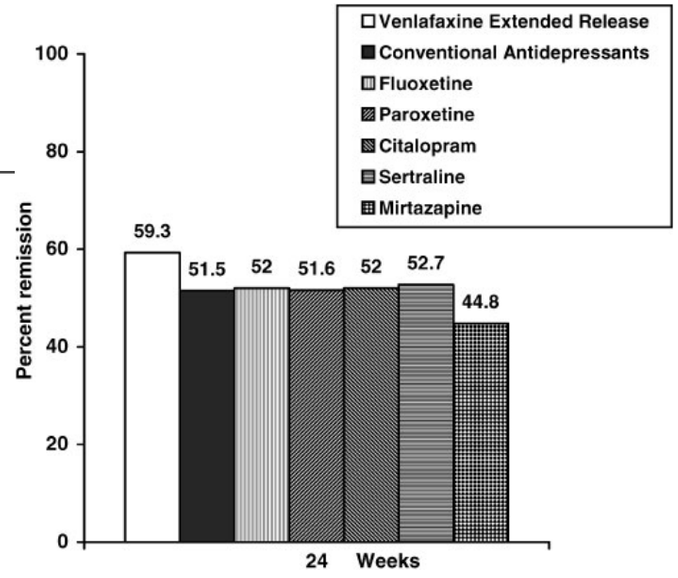
- => SSRI -> Venlafaxin ist effektiv
  - Effektgrösse wahrscheinlich klein

Switch SSRI -> Mirtazapin



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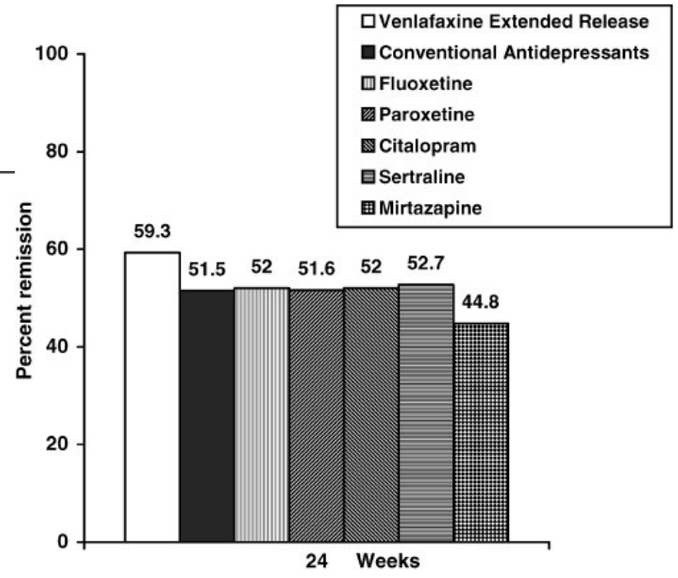
Switch SSRI -> Mirtazapin

- Noch weniger Daten



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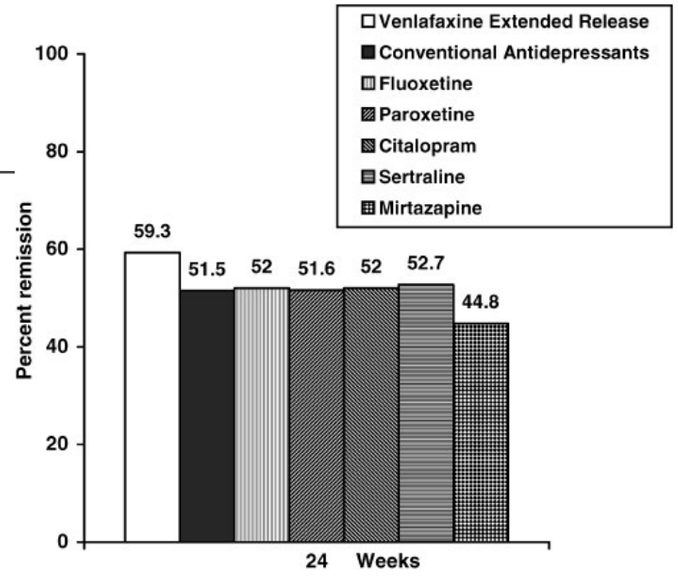

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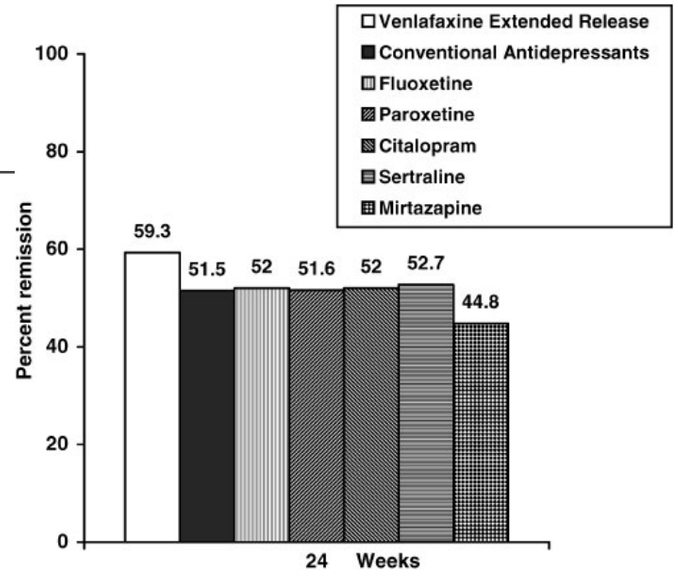

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- Unblinded
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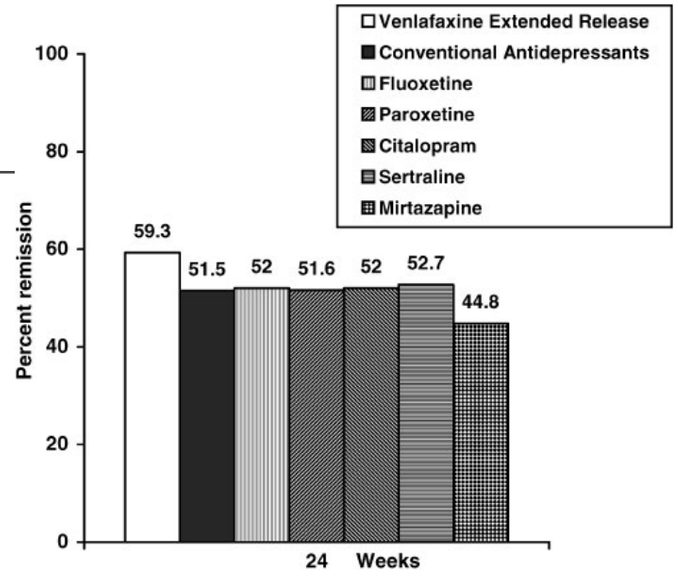

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  - ARGOS (n=3097) Venlafaxin 59.3% vs Mirtazapin 44.8%
- => SSRI -> Mirtazapin möglicherweise effektiv.

Switch SSRI -> TCA

- Noch weniger Daten
- Keine DB-RCTs
- Unblinded
  - STAR*D Step 3 Mirtazapin = Nortryptilin
  - Souery et al., 2011 - switch SSRI/TCA, aber kein Vergleich.

- => Unklare Datenlage für switch von SSRI zu TCA

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  - Souery et al., 2011 - switch SSRI/TCA, aber kein Vergleich.

- => Unklare Datenlage für switch von SSRI zu TCA

  - **MOA** - Daten existieren nur für switch von TCA, nicht von SSRI.
  - STAR*D: MOA=Trancyclopromine. Weniger gut toleriert. Nicht besser für atypische Depression.

Strategien

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  - zu TCA — ?
  - zu MOA — nein?
- Augmentation
  - Lithium
  - Triiodothyronin
  - Atypikum
- Kombination
  - Mirtazapin/Mianserin + SSRI/SNRI
  - Desipramine + SSRI/SNRI

Lithium Augmentation

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- TCAs - gute Datenlage
  - Meta-analyse Crossley & Bauer 2007. 10(?) Studien. NNT ~4.

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- SSRIs
  - Katona et al., 1995
    - DB RCT: Li+Fluoxetine = Li+Lofepramin > Pla+Flu/Lof. n=61
  - Baumann et al., 1996
    - DB RCT: Citalopram + Li 60% > Citalopram + Pla 14% n=24
  - STAR*D
    - Step 3. n=142. Li augm 15.9% vs T3 augm 24.7%

- Bauer et al., 2013 (WFSBP): überzeugend
- Connolly & Thase 2011: ungenügend

Andere Augmentationen

- T3
  - Evidenzbasis nicht stark.
  - STAR*D: nicht besser als Li, aber mehr Nebeneffekte und daher mehr drop-out.

- Buspiron, Pindolol
  - keine Effekte

- Stimulantien (Modafinil, methylphenidat)
  - marginaler Effekt in ‘enriched sample’ mit Müdigkeit

Augmentation mit Atypika

- Kommerzielle Interessen -> substantielle Studien

- Theoretisch via 5HT
  - 2A
  - 1A partielle Agonisten: Ziprasidon, Aripiprazol
  - NAT: Quetiapin, Ziprasidon

- Nebeneffekte
  - Tardive Dyskinasien, EPS
  - Metabolische / kardiologische Komplikationen

Aripiprazol

Table V. Aripiprazole augmentation of current-generation antidepressants in randomized, placebo-controlled trials

Trial (year)	Duration of double-blind augmentation (weeks)	Response to aripiprazole augmentation[a] [rate (%)]	Response to placebo augmentation [rate (%)]	NNT[a]
Berman et al.[45] (2007)	6	61/182 (33.5)	42/176 (23.9)	10
Marcus et al.[46] (2008)	6	62/191 (32.4)	33/190 (17.4)	6.66
Berman et al.[48] (2009)	6	82/177 (46.3)	46/172 (26.7)	5

a Response is defined as 50% reduction in Montgomery-Åsberg Depression Rating Scale.

NNT = number needed to treat for one clinical response.

- 8 Wochen SSRI non-response.
- 6 Wochen DB-RCT 2-20mg Arip
- pooled n=749
- 3 trials, 3 positive Resultate
- MADRS 3 Punkte besser, Remission 25.7% vs 15.4%

- Akathisie und Unruhe
- Gewichtszunahme ca 1kg mehr als SSRI Weiterfuhrung

Connolly & Thase 2011

Quetiapin

Table III. Quetiapine extended-release augmentation of current-generation antidepressants in randomized, placebo-controlled trials

Trial (year)	Duration of double-blind augmentation (weeks)	Response rate with quetiapine 150 mg augmentation[a] [rate (%)]	Response rate with quetiapine 300 mg augmentation [rate (%)][b]	Response rate with placebo augmentation [rate (%)]	NNT at 300 mg dose[a]
Bauer et al.[36] (2009)	6	92/166 (55.4)	93/166 (56)	74/160 (46.3)	8.7
El-Khalili et al.[37] (2010)	6	74/143 (51.7)	86/146 (58.9)	66/143 (46.2)	7.8

a Response is defined as 50% reduction in Montgomery-Åsberg Depression Rating Scale.

b Only the 300 mg dose was statistically superior.

NNT = number needed to treat for one clinical response.

nur 300mg / diem signifikant

- Gewicht, LDL & Trig, Glucose alle erhoht

Connolly & Thase 2011

Olanzapin + Fluoxetin

Olanzapin + Fluoxetin

Table II. Olanzapine/fluoxetine combination (OFC) compared with fluoxetine (FLX) alone in randomized, placebo-controlled trials

Trial (year)	Duration of double-blind augmentation (weeks)	Response rate with OFC [rate (%)][a]	Response rate with fluoxetine [rate (%)][a]	NNT	Notes
Shelton et al.[32] (2001)	8	6/10 (60)	1/10 (10)	2	Also included OLZ-only group. OFC vs FLX not statistically significant
Shelton et al.[33] (2005)	8	40/146 (27.4)	41/142 (28.9)	NA	OFC compared with FLX started simultaneously. Also included OLZ-only group. OFC vs FLX not statistically significant
Corya et al.[34] (2006)	12	100/243 (41.2)	19/60 (31.6)	NA	OFC compared with FLX started simultaneously. Also included OLZ-only group. OFC vs FLX not statistically significant
Thase et al.[35] (2007)	8	Study 1: 37/101 (36.6) Study 2: 43/97 (44.3) Total: 80/198 (40.4)	Study 1: 30/102 (29.4) Study 2: 30/101 (29.7) Total: 60/203 (29.6)	9.26	Pooled results statistically significant

a Response is defined as 50% reduction in Montgomery-Åsberg Depression Rating Scale.

NA = no significant advantage found; **NNT** = number needed to treat for one clinical response; **OLZ** = olanzapine.

Connolly & Thase 2011

Risperidon

- Risperidon

Table IV. Risperidone augmentation of current-generation antidepressants in randomized, placebo-controlled trials

Trial (year)	Duration of double-blind augmentation (weeks)	Response to risperidone augmentation [rate (%)]	Response to placebo augmentation [rate (%)]	NNT	Definition of response
Mahmoud et al.[40] (2007)	4	49/106 (46.2)	33/112 (29.5)	8.3	50% reduction in HDRS at 4 weeks
Keitner et al.[41] (2009)	4	35/64 (54.7)	10/30 (33.3)	4.65	50% reduction in MADRS at 4 weeks
Rapaport et al.[42] (2006)	24	57/122 (46.7)	54/119 (45.4)	No significant difference	Remaining free of depressive relapse at 24 weeks

HDRS = Hamilton Depression Rating Scale; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **NNT** = number needed to treat for one clinical response.

Connolly & Thase 2011

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HDRS = Hamilton Depression Rating Scale; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **NNT** = number needed to treat for one clinical response.

Connolly & Thase 2011

Augmentation mit Atypika

- SSRI + Aripiprazol NNT ~7

- SSRI + Quetiapin NNT ~8
- SSRI + Risperidon NNT ~6, aber kurzfristig
- Fluoxetin + Olanzapin NNT ~10

- Unklar ob Atypika zur Rezidivprophylaxe beitragen

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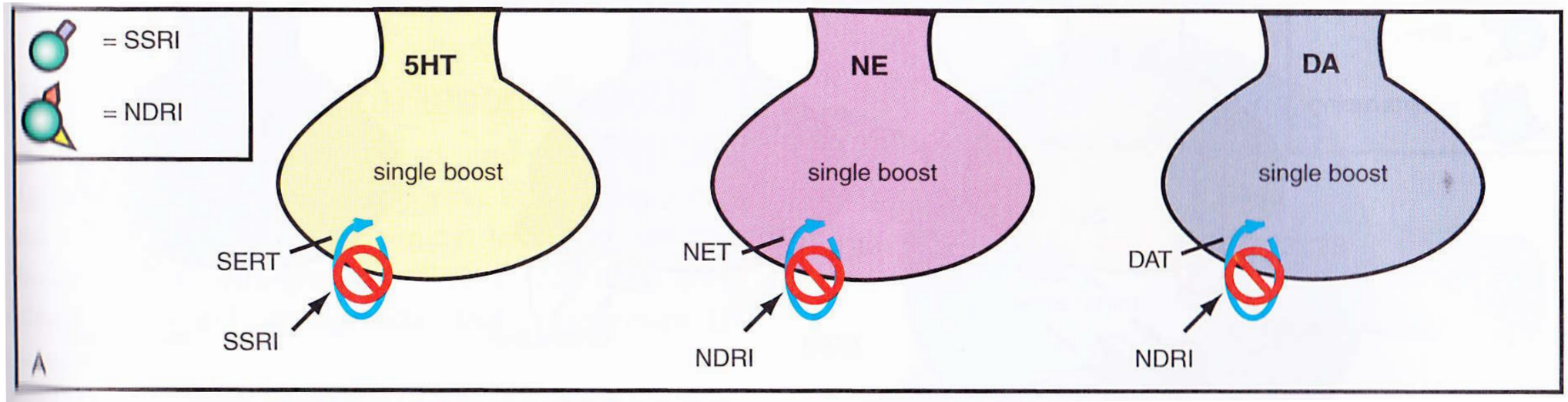
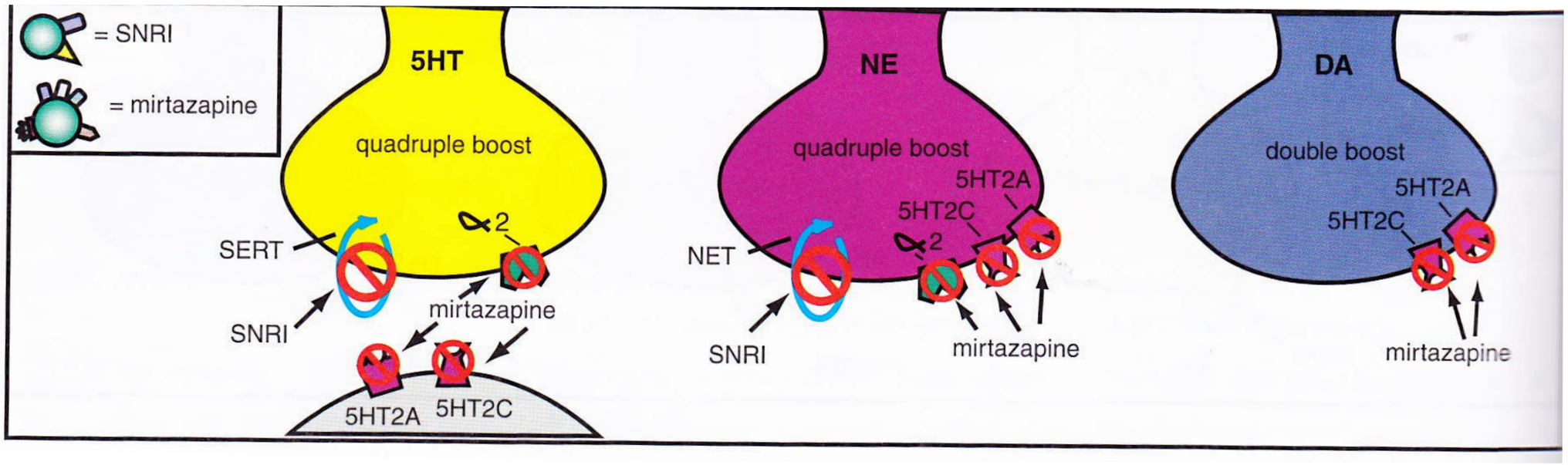
  - zu anderem SSRI/SNRI — SNRI > SSRI
  - zu Mirtazapin — ?
  - zu TCA — ?
  - zu MOA — nein?
- Augmentation
  - Lithium — nach TCA
  - Triiodothyronin — nein?
  - Atypikum — aripiprazol - NNT ca 7
- Kombination
  - Mirtazapin/Mianserin + SSRI/SNRI
  - Desipramine + SSRI/SNRI

Kombinationen

- Triple action



- Californian rocket fuel



Stahl, 2013

Californian rocket fuel minor

- Mirtazepine
  - 1 DB RCT, n=26 non-responders nach 4 Wochen SSRI
  - SSRI+Pla / SSRI+Mirtazepin
  - Remission 45.5% vs 13.3%. NNT = 3

  - Ko-medikation: 2 RCTs. NNT 3-5.

- Mianserin
  - 1 DB RCT, n=104 non-responders nach 6 Wochen Fluox.
  - Fluox+Pla / Fluox+MIA / Pla+MIA
  - Remission: 44% / 36% / 18%. NNT = 4

Triple action

- Bupropion + SSRI oder SNRI
  - Case studies.
  - Keine DB RCTs.

- Desipramine + Fluoxetin
  - 3 DB RCTs. 1 positives Resultat, 2 negative.
  - Beide 2D6 Substrate

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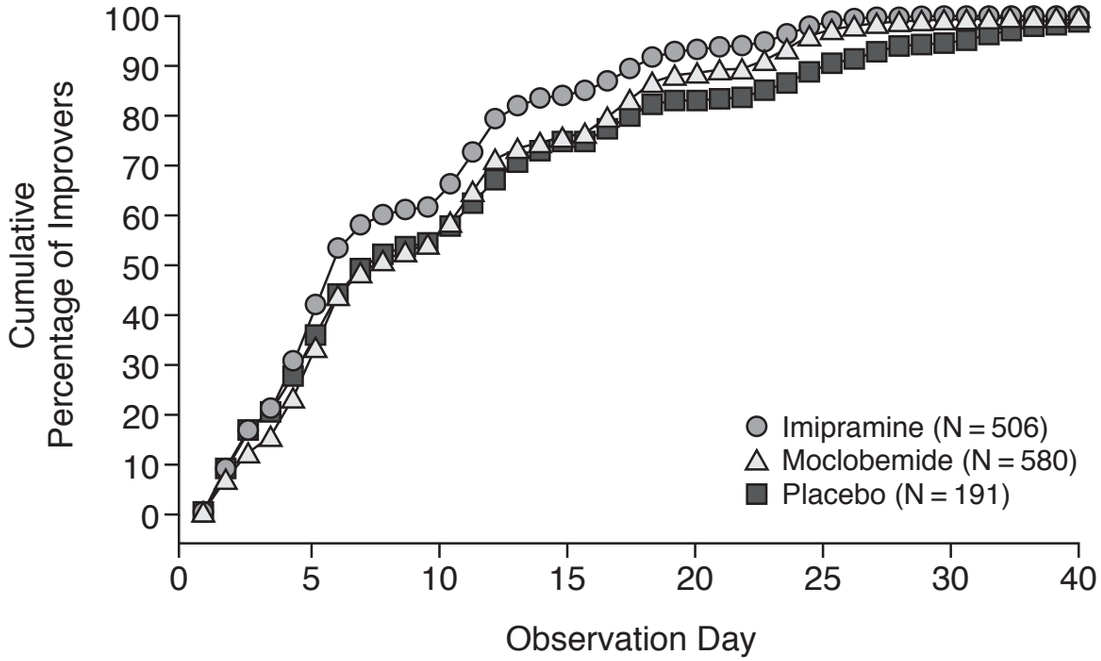
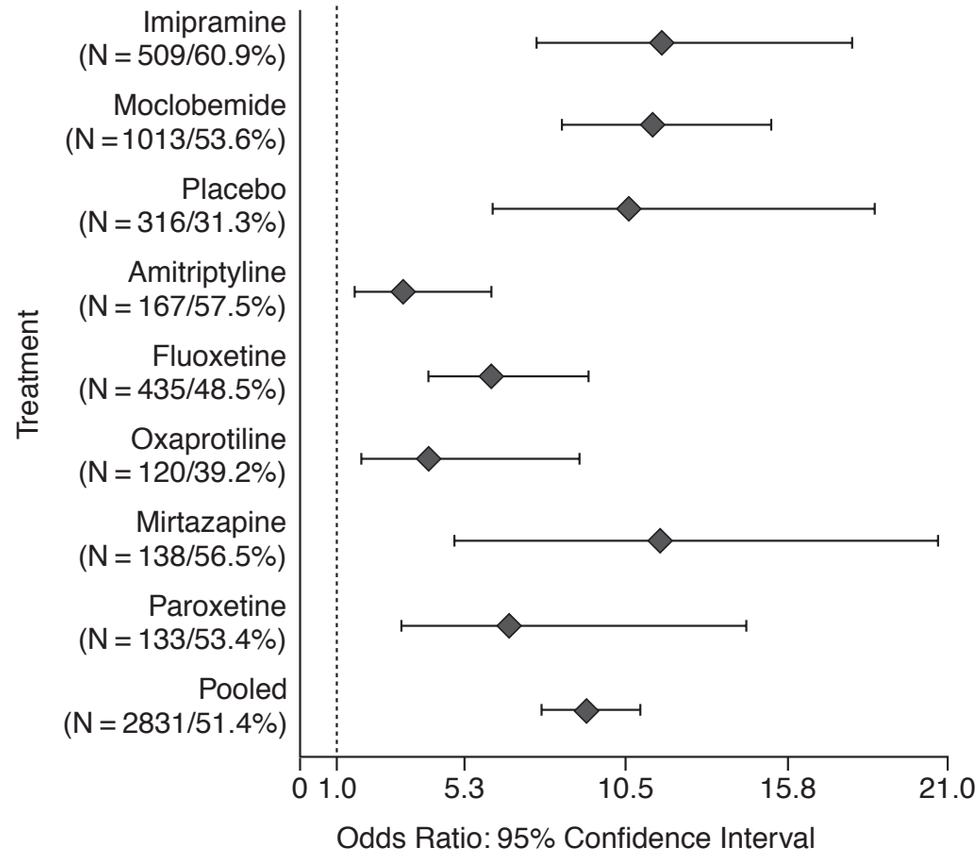
Literatur

- Connolly & Thase 2011: If at first you don't succeed. *Drugs 71(1):43-64*
- Bauer et al., 2013: WFSBP Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorder. *World J Biol Psych 13:334-385*
- Fava and Rush 2006: Current status of augmentation and combination treatments for major depressive disorder: a literature review and a proposal for a novel approach to improve practice. *Psychother Psychosom 75:139-153*
- NICE Clinical Guideline 80: Depression in Adults. Oktober 2009.
- Komossa, K., Depping, A. M., Gaudchau, A., Kissling, W., & Leucht, S. (2010). Second−generation antipsychotics for major depressive disorder and dysthymia. *The Cochrane Library*.

Wann hat's nicht geklappt?

- Ansprechen innerhalb von 14 Tagen ersichtlich

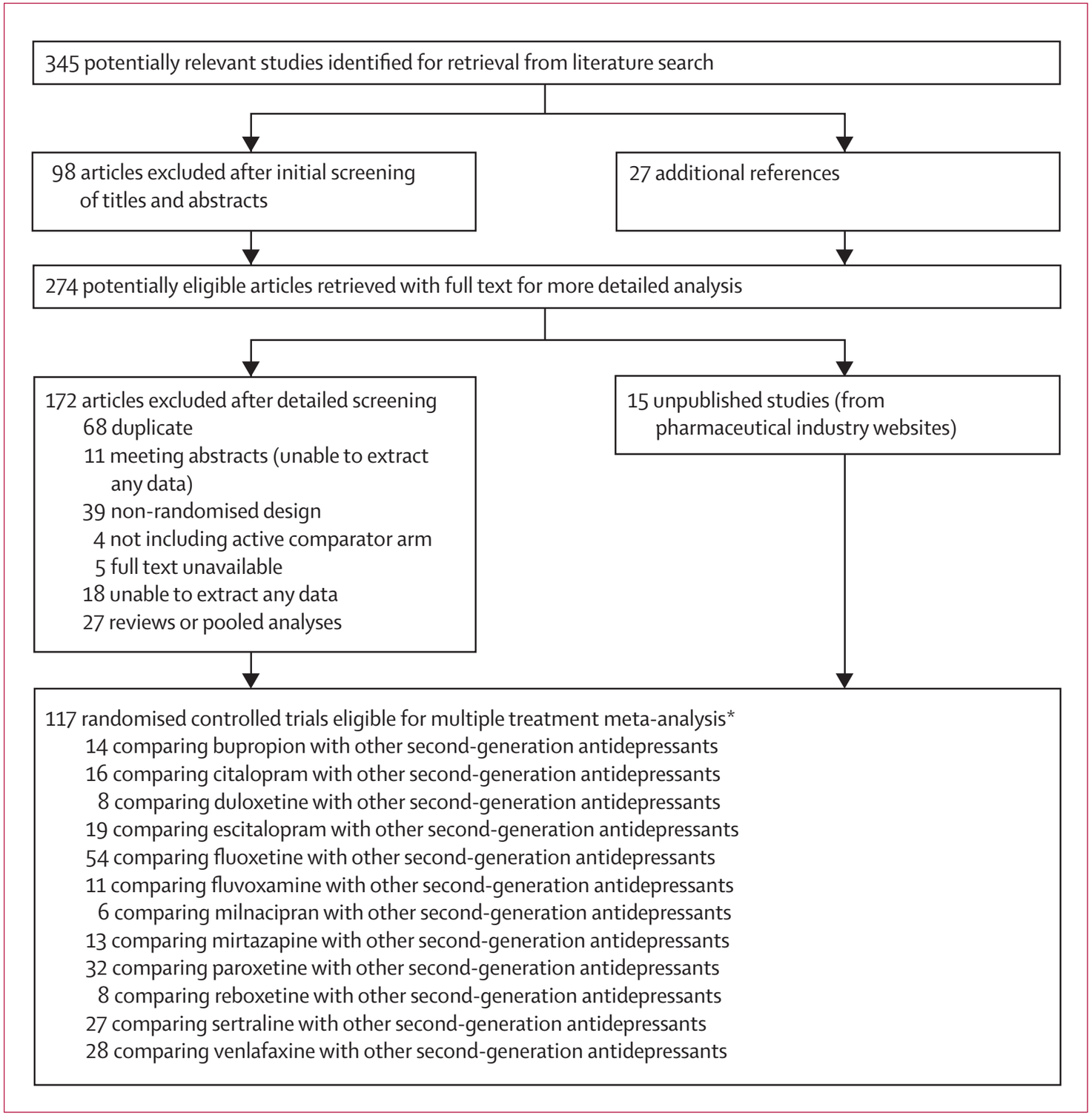




Stassen et al., 2007

- <10% werden danach noch responders Szegedi et al., 2003, 2009

Cipriani et al. 2009



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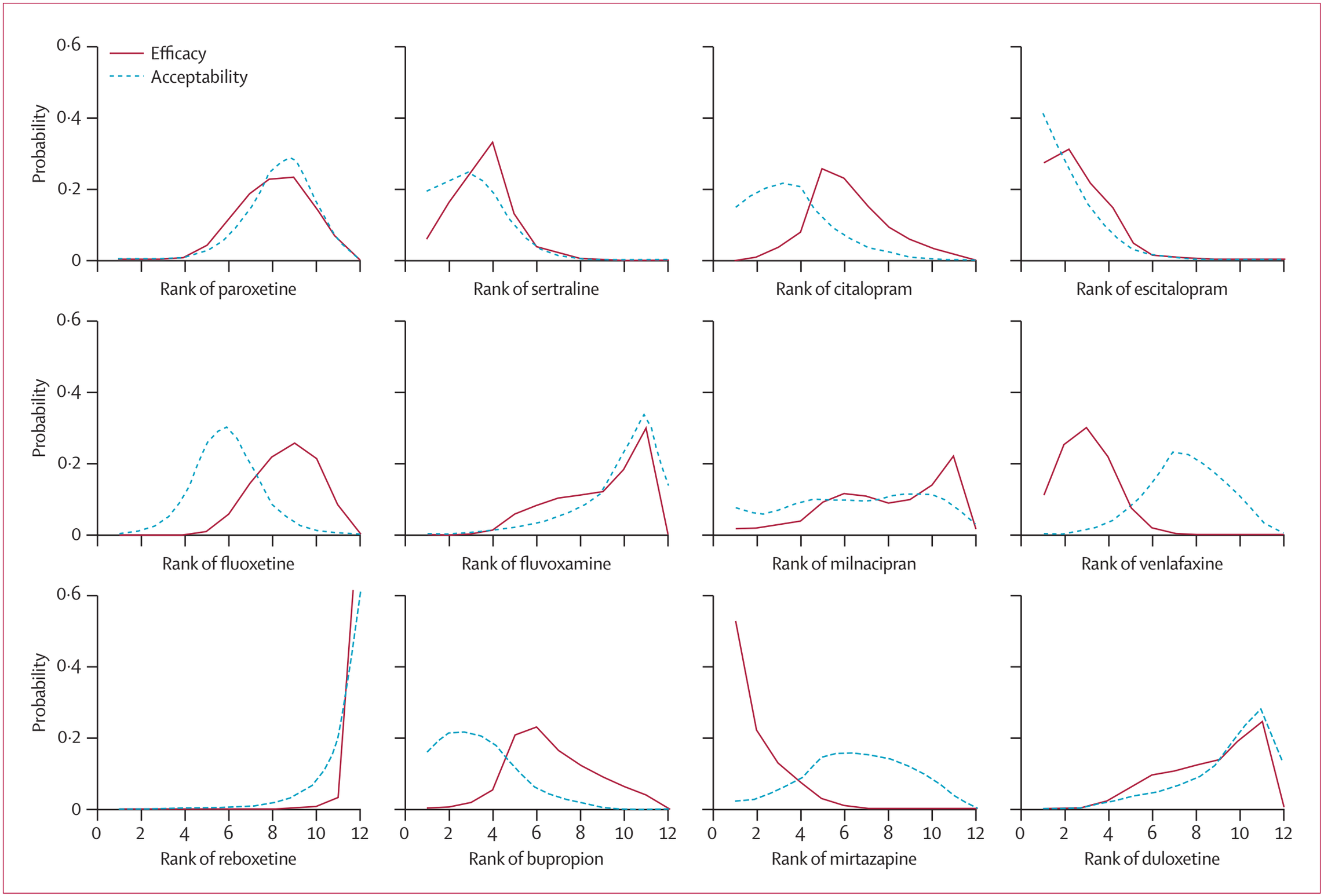

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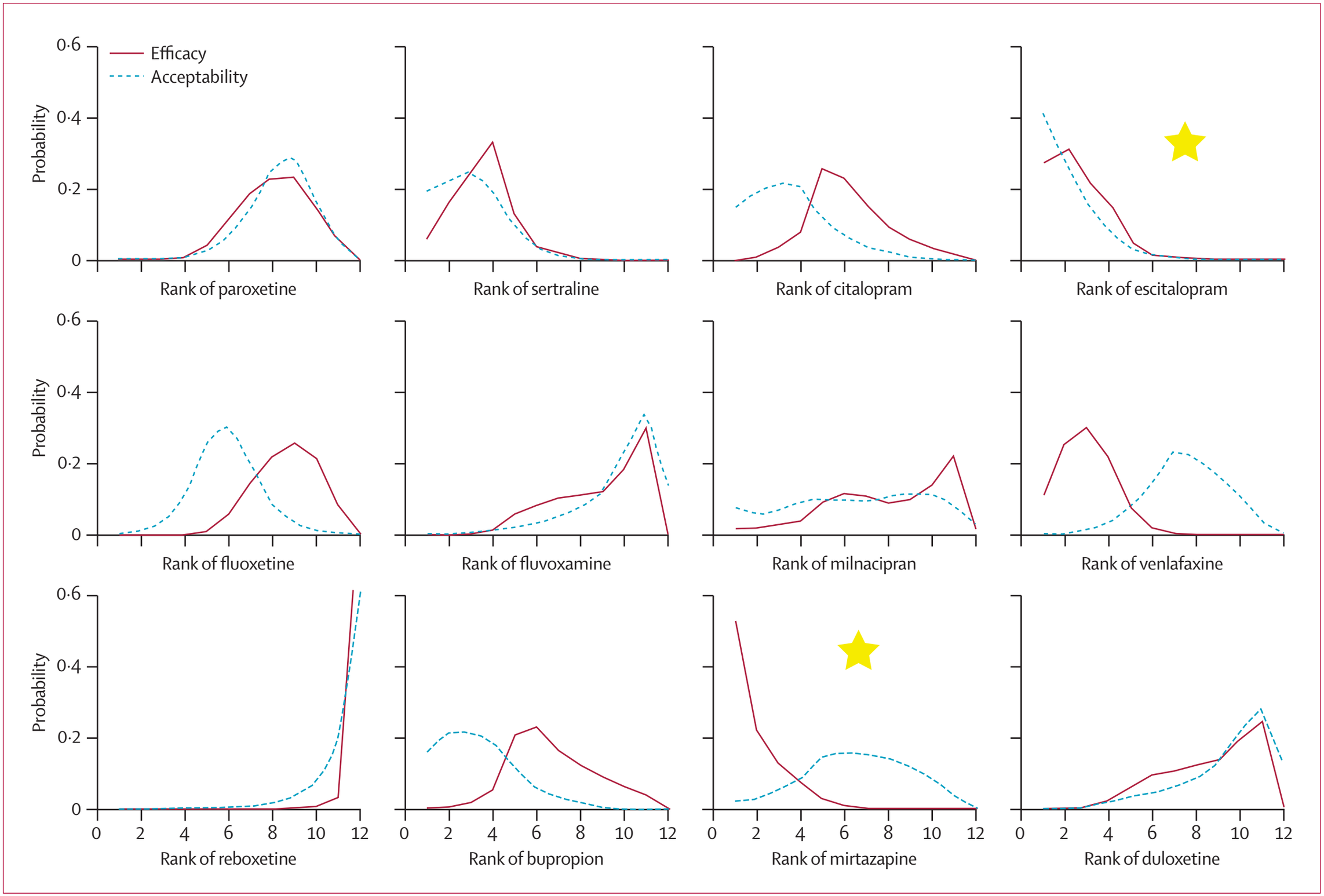

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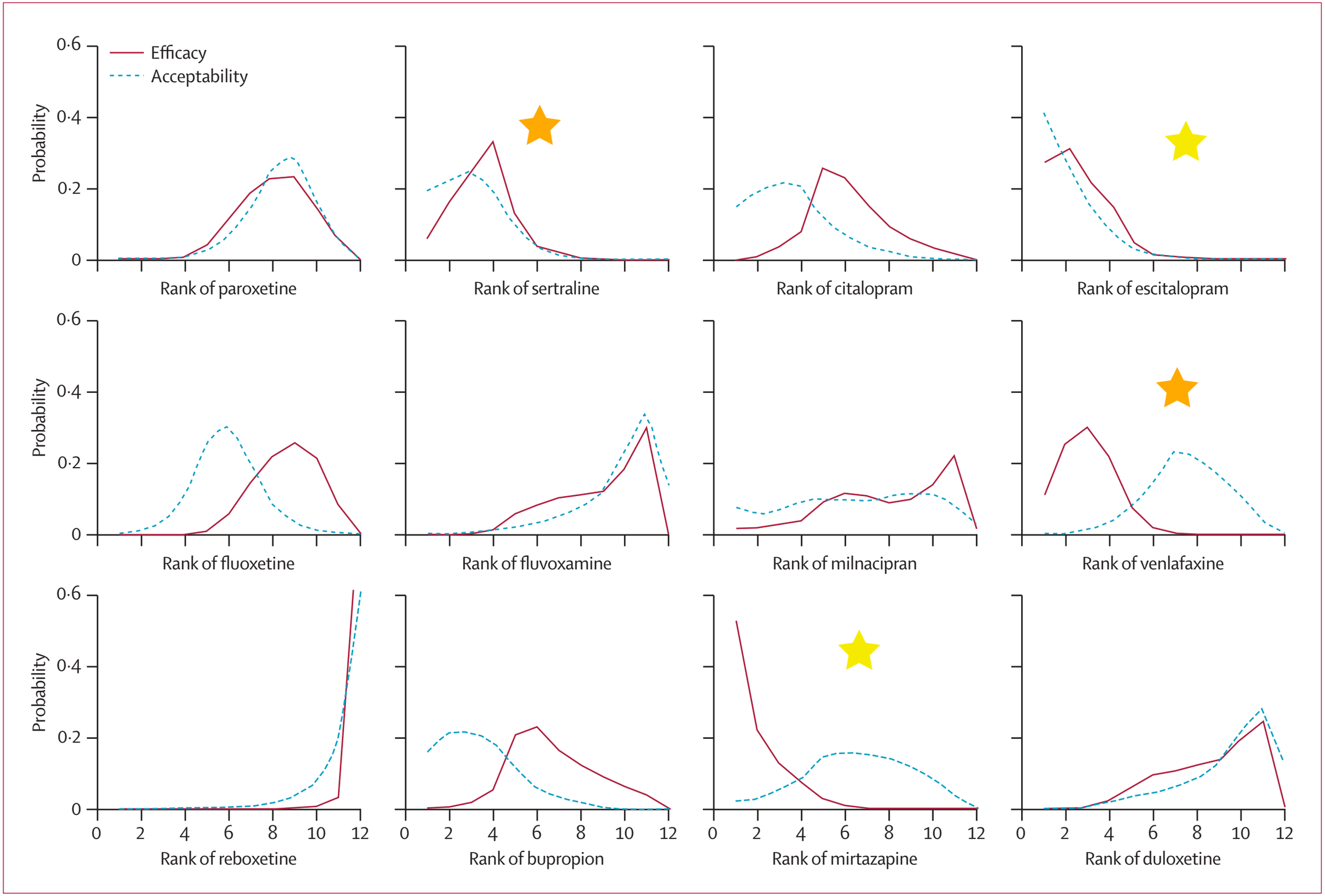


Rush et al., 2006

Step 1

Enrolled (N=4,041)

No postbaseline visit (N=370)

Citalopram (N=3,671) — Level 1

Exit (N=766)

Follow-up (N=1,475)

Step 2[a]

Bupropion SR (N=239)

Sertraline (N=238)

Venlafaxine XR (N=250)

Citalopram plus bupropion SR (N=279)

Citalopram plus buspirone (N=286)

Citalopram plus cognitive therapy (N=85)

Cognitive therapy (N=62) — Level 2

Exit (N=389)

Follow-up (N=544)

Exit (N=38)

Follow-up (N=78)

Step 3

Nortriptyline (N=116)

Mirtazapine (N=110)

Lithium augmentation (N=63)

T_3 augmentation (N=70) — Level 3

Bupropion SR (N=15)

Venlafaxine XR (N=16) — Level 2A[b]

Exit (N=160)

Follow-up (N=94)

Exit (N=5)

Follow-up (N=8)

Step 4

Tranylcypromine (N=55)

Venlafaxine XR plus mirtazapine (N=50) — Level 4

Nortriptyline (N=5)

Mirtazapine (N=4)

Lithium augmentation (N=6)

T_3 augmentation (N=3) — Level 3

Exit (N=9)

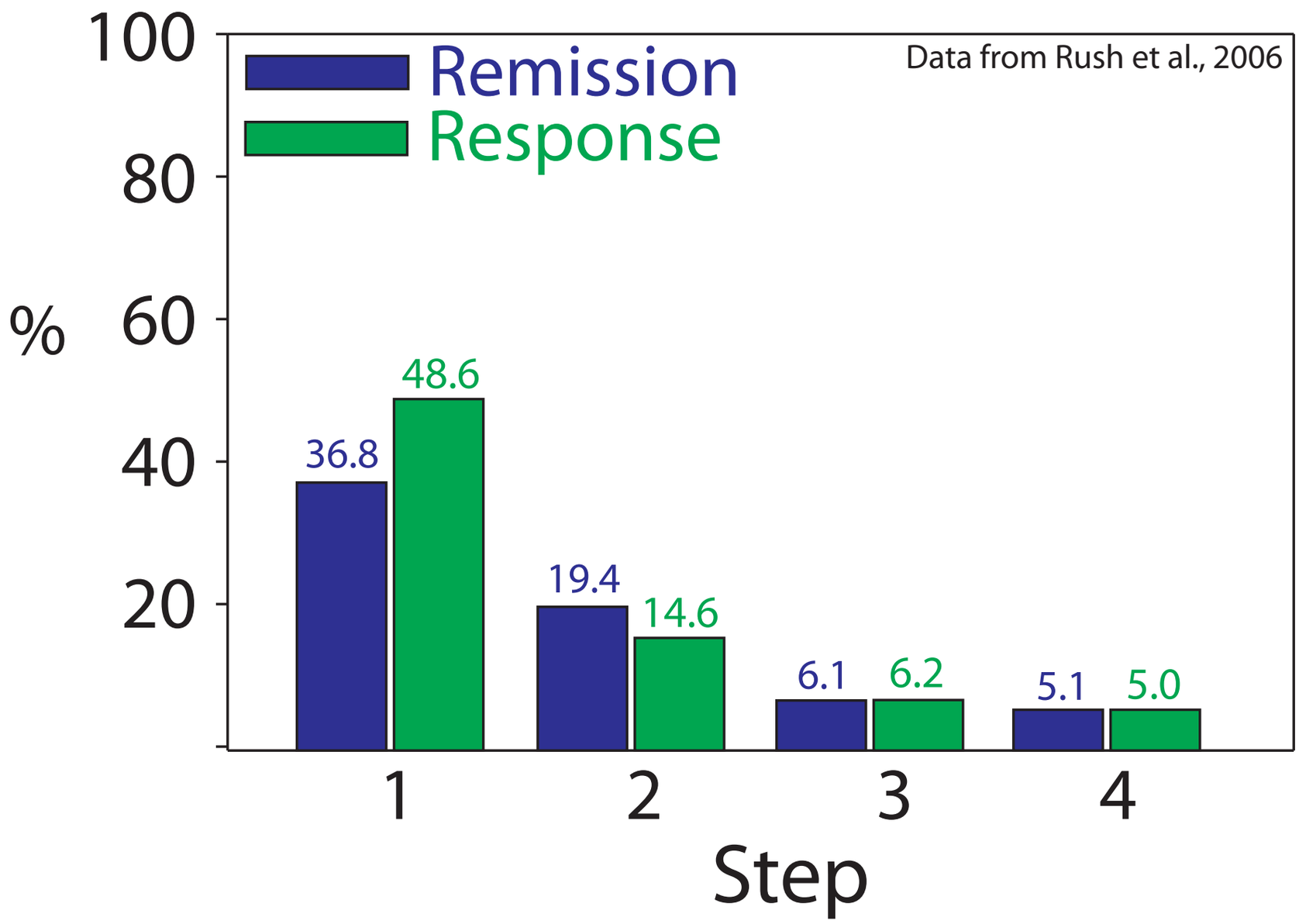
Follow-up (N=5)

Step 5[b]

Tranylcypromine (N=3)

Venlafaxine XR plus mirtazapine (N=1) — Level 4

STAR*D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Li Metaanalysis: Bauer and Crossley 2007

Table 2. Randomized Double-Blind Lithium Augmentation Studies

Study	Subjects	Antidepressant Treatment	Lithium Dosage (serum level) and Duration	Response Criteria
Heninger et al (1983)[26]	14 UP, 1 BP, 12 F, 3 M, mean age = 50 y	Various TCAs and tetracyclics	900–1200 mg/d (0.5–1.1 mmol/L), 12 d	Decrease of 2 or more points on SCRS
Kantor et al (1986)[22]	7 UP, sex NR, mean age NR	Various TCAs	900 mg/d, 48 h	≥ 40% decrease in HAM-D
Zusky et al (1988)[23]	16 UP, 13 F, 3 M, mean age = 45 y	Various TCAs and MAOIs	300 mg/d first week, 900 mg/d second week, 14 d	Final HAM-D ≤ 7
Schöpf et al (1989)[28]	18 UP, 9 BP, 19 F, 8 M, mean age = 54 y	Various antidepressants	600–800 mg/d (0.6–0.8 mmol/L), 7 d	≥ 50% decrease in HAM-D
Browne et al (1990)[29]	14 UP, 3 BP, 10 F, 7 M, mean age = 42 y	Various TCAs and tetracyclics	900 mg/d, 48 h	≥ 50% decrease in HAM-D
Stein and Bernadt (1993)[24]	34 UP, 27 F, 7 M, mean age = 47 y	Various TCAs	250 mg/d, 21 d	≥ 50% decrease in HAM-D
Joffe et al (1993)[25]	33 UP, 18 F, 15 M, mean age = 37 y	Various TCAs	900 mg/d (> 0.55 mmol/L), 14 d	≥ 50% decrease in HAM-D
Katona et al (1995)[30]	N = 61, polarity NR, 35 F, 26 M, mean age = 40 y	SSRIs and TCAs	800 mg/d (0.6–1 mmol/L), 42 d	≥ 50% decrease in HAM-D
Baumann et al (1996)[27]	23 UP, 1 BP, 17 F, 7 M, mean age = 41 y	Citalopram	800 mg/d (0.5–0.8 mmol/L), 7 d	≥ 50% decrease in HAM-D
Nierenberg et al (2003)[4]	35 UP, 16 F, 19 M, mean age = 38 y	Nortriptyline	900 mg/d	≥ 50% decrease in HAM-D

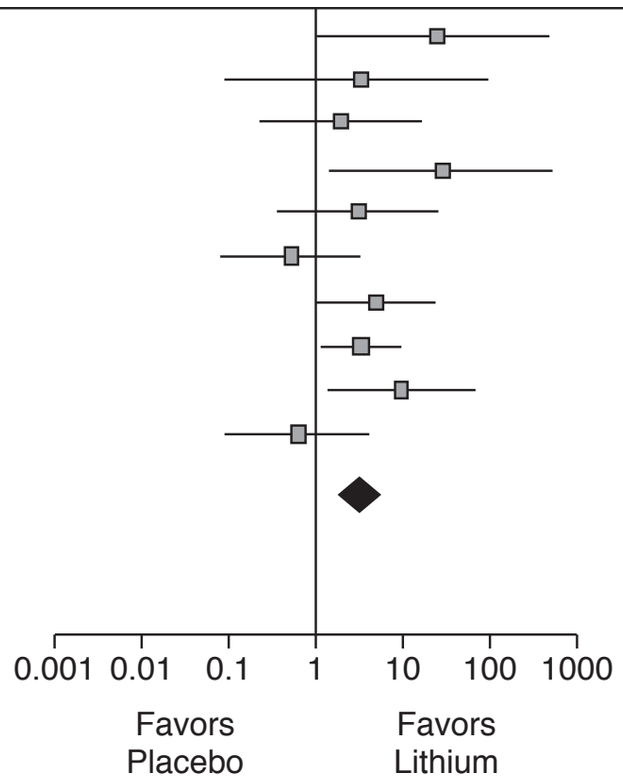
Abbreviations: BP = bipolar, F = female, HAM-D = Hamilton Rating Scale for Depression, M = male, MAOI = monoamine oxidase inhibitor, NR = not reported, SCRS = Short Clinical Rating Scale, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, UP = unipolar.

Li Metaanalysis: Bauer and Crossley 2007

Figure 2. Meta-Analysis of Lithium Augmentation Studies[a]

Study	Lithium, N/N	Control, N/N	Fixed Effects OR and 95% CI	Fixed Effects OR (95% CI)
Heninger et al (1983)[26]	5/8	0/7		23.57 (1.00 to 556.08)
Kantor et al (1986)[22]	1/4	0/3		3.00 (0.09 to 102.05)
Zusky et al (1988)[23]	3/8	2/8		1.80 (0.21 to 15.41)
Schöpf et al (1989)[28]	7/14	0/13		27.00 (1.35 to 541.57)
Browne et al (1990)[29]	3/7	2/10		3.00 (0.35 to 25.87)
Stein and Bernadt (1993)[24]	2/16	4/18		0.50 (0.08 to 3.19)
Joffe et al (1993)[25]	9/17	3/16		4.88 (1.01 to 23.57)
Katona et al (1995)[30]	15/29	8/32		3.21 (1.09 to 9.48)
Baumann et al (1996)[27]	6/10	2/14		9.00 (1.27 to 63.89)
Nierenberg et al (2003)[4]	2/18	3/17		0.58 (0.08 to 4.01)
Total	53/131	24/138		3.11 (1.80 to 5.37)

Test for Heterogeneity: $\chi^2 = 11.90$, df = 9, p = .22, $I^2 = 24.4\%$
Test for Overall Effect: Z = 4.06, p < .0001



[a]Pooling of patients responding to augmentation therapy. Fixed effects model used.[9]

Baldomero et al., ARGOS study