The Paradox of Choice – Why More is Less for Treating Treatment-Resistant Depression

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The MEDS Conference

February 11, 2017

Faculty/Presenter Disclosure

- **Faculty**: Christine Leong and James Bolton

- **Relationships with commercial interests**:
  - Not applicable

Mitigating Potential Bias

- Not applicable

CASE

- **43 year-old female** with moderate to severe **depression** (12 years)
- Trialed monotherapy:
  - Citalopram (6 months – no response)
  - Paroxetine (1 month – side effects)
  - Venlafaxine XR (8 months – minimal response)

CASE

Which of the following would you recommend next?

A. Combination venlafaxine XR plus mirtazapine

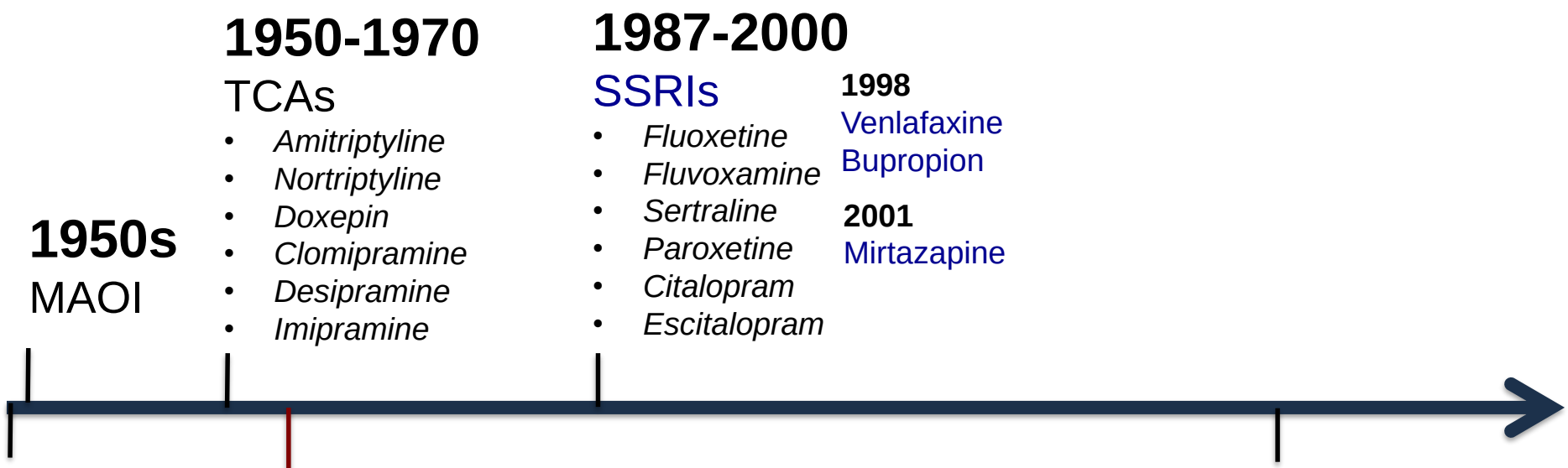
B. Switch to fluoxetine

C. Switch to bupropion SR

D. Augment with thyroid hormone

E. Augment with aripiprazole

History of Antidepressants



Pre-1950
Chloral hydrate
Barbiturates
Amphetamines
Opioids

1950s
MAOI

1960s
Iproniazid (*liver/renal*)
MAOI (*liver/HTN crisis*)

1950-1970
TCAs
- *Amitriptyline*
- *Nortriptyline*
- *Doxepin*
- *Clomipramine*
- *Desipramine*
- *Imipramine*

1987-2000
SSRIs
- *Fluoxetine*
- *Fluvoxamine*
- *Sertraline*
- *Paroxetine*
- *Citalopram*
- *Escitalopram*

1998
Venlafaxine
Bupropion

2001
Mirtazapine

2014-2015
- Vortioxetine
- Levomilnacipran
- Vilazodone

J Clin Psychopharmacol 2007;27(6):555; Can J Psych 2016;61(9):540-560; J Clin Psychopharmacol 2005;25:336-41.

History of Antidepressants

1950-1970

TCAs

- *Amitriptyline*
- *Nortriptyline*
- *Doxepin*
- *Clomipramin*
- *Desipramine*
- *Imipramine*

1987-2000

SSRIs

- *Fluoxetine*
- *Fluvoxamine*
- *Sertraline*

1998

Venlafaxine

Bupropion

2001

1950s

MAOI

Pre-1950

Chloral hydrate
Barbiturates
Amphetamines
Opioids

1960s

Iproniazi

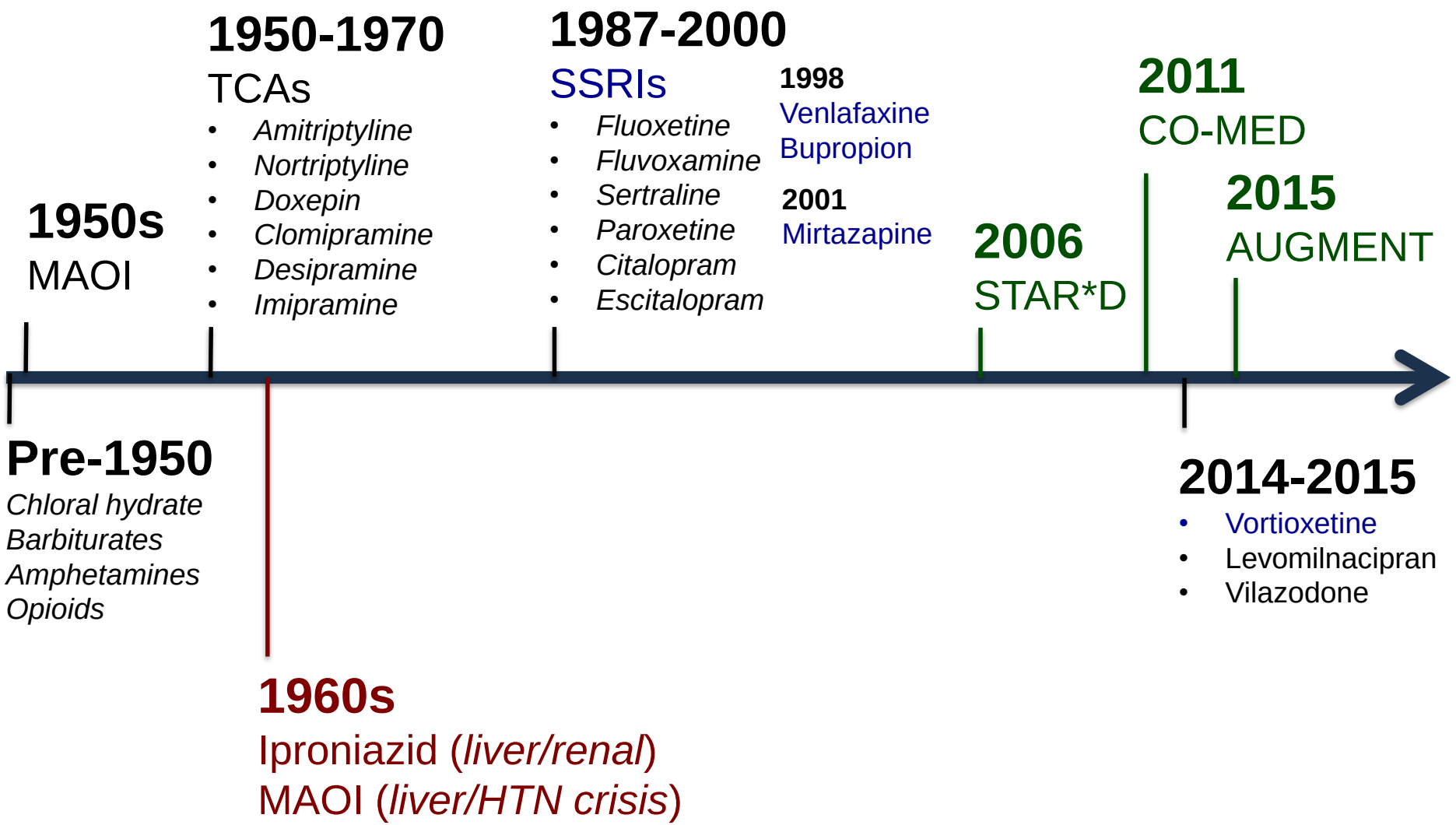
MAOI (*li*

Antidepressant Trial

- 6-12 weeks
- Assess improvement in ~4 weeks:
  - **Response: ≥50%**
  - **Partial Response: 20-50%**
  - **No Response <20%**
- **~30-50%** do not achieve remission despite adequate antidepressant trials

J Clin Psychopharmacol 2007;27(6):555; Can J Psych 2016;61(9):540-560; J Clin Psychopharmacol 2005;25:336-41.

History of Antidepressants



J Clin Psychopharmacol 2007;27(6):555; Can J Psych 2016;61(9):540-560; J Clin Psychopharmacol 2005;25:336-41.

Treatment-Resistant Depression

- Failed adequate trials of **≥2 antidepressants**
- Prevalence difficult to estimate
- **Poorer outcome** and **recurrence** risk

Several options
Conflicting data
No expert consensus
Limited guidance

First-line:
- SSRI
- SNRI
- Bupropion SR
- Mirtazapine

Next Step?
- Switch (same class)
- Switch (out-of-class)
- Combination
- Augmentation (SGA, Li, T3/T4, methylphenidate, propranolol)

CANMAT 2016; NICE 2009; APA 2010

Clinical Practice Guidelines

CANMAT 2016

"The decision between switching and adjunctive strategies should be individualized based on clinical factors." (Level 3)

NICE 2009 (updated 2016)

"…evidence for within or between class switching is weak. SSRI or better tolerated…antidepressant preferred."

"If patient is informed about and prepared to tolerate…combining/augmenting…"

Li
SGA (A/O/Q/R)
AD

APA 2010

"Change to a **non-MAOI AD** in the same

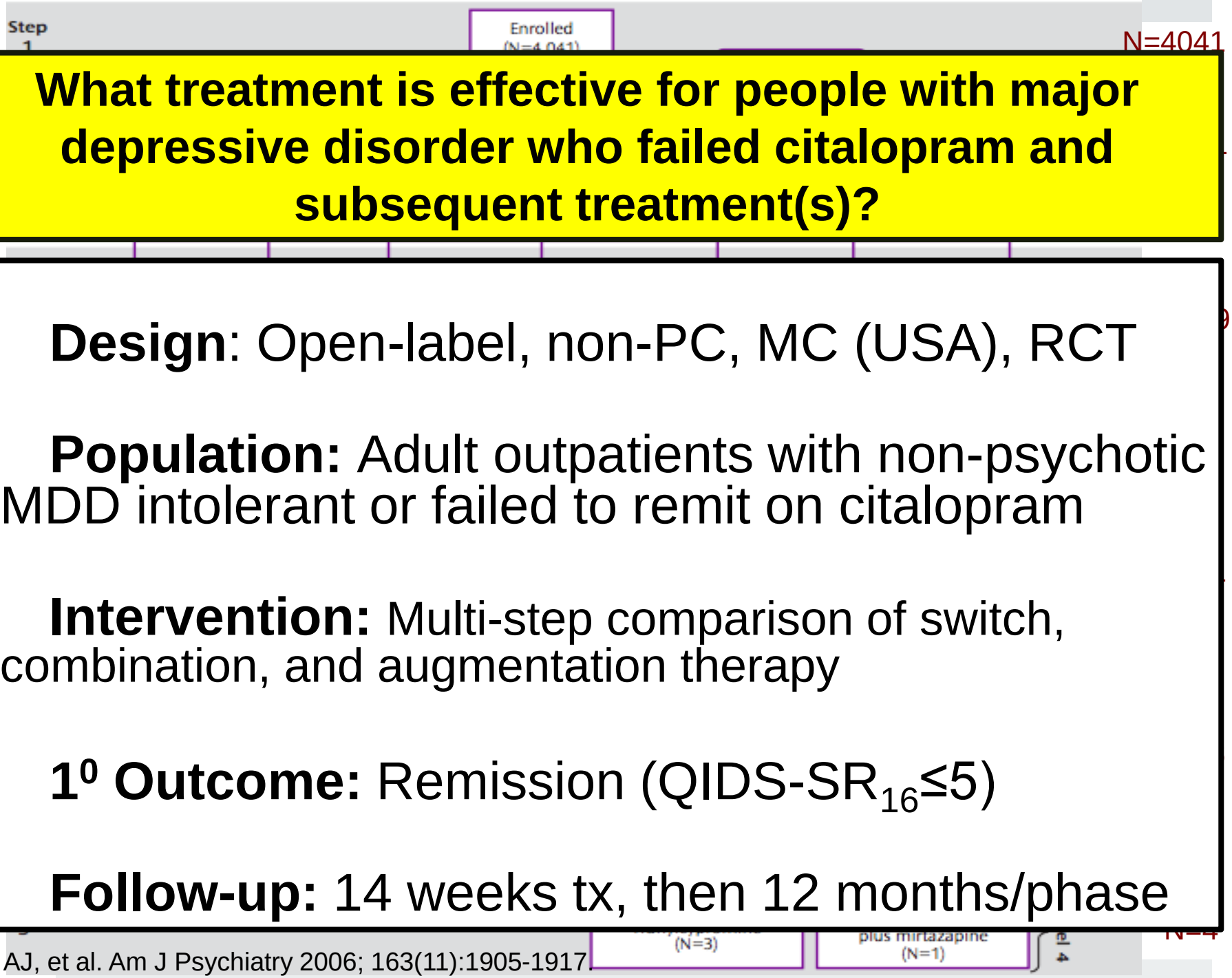
Non-MAOI AD (different class)
Li
T3/T4
SGA

Studies

- STAR*D 2006 } **5-Steps Switch vs. Combo vs. Augment**
- Zhou et al. 2015 Network Meta-Analysis } **Augmentation**

Studies

- **STAR*D 2006**
- *Zhou et al. 2015 Network Meta-Analysis*



What treatment is effective for people with major depressive disorder who failed citalopram and subsequent treatment(s)?

- **Design**: Open-label, non-PC, MC (USA), RCT
- **Population:** Adult outpatients with non-psychotic MDD intolerant or failed to remit on citalopram
- **Intervention:** Multi-step comparison of switch, combination, and augmentation therapy
- **1^0 Outcome:** Remission ($QIDS\text{-}SR_{16} \leq 5$)
- **Follow-up:** 14 weeks tx, then 12 months/phase

Rush AJ, et al. Am J Psychiatry 2006; 163(11):1905-1917.

POPULATION DEMOGRAPHICS

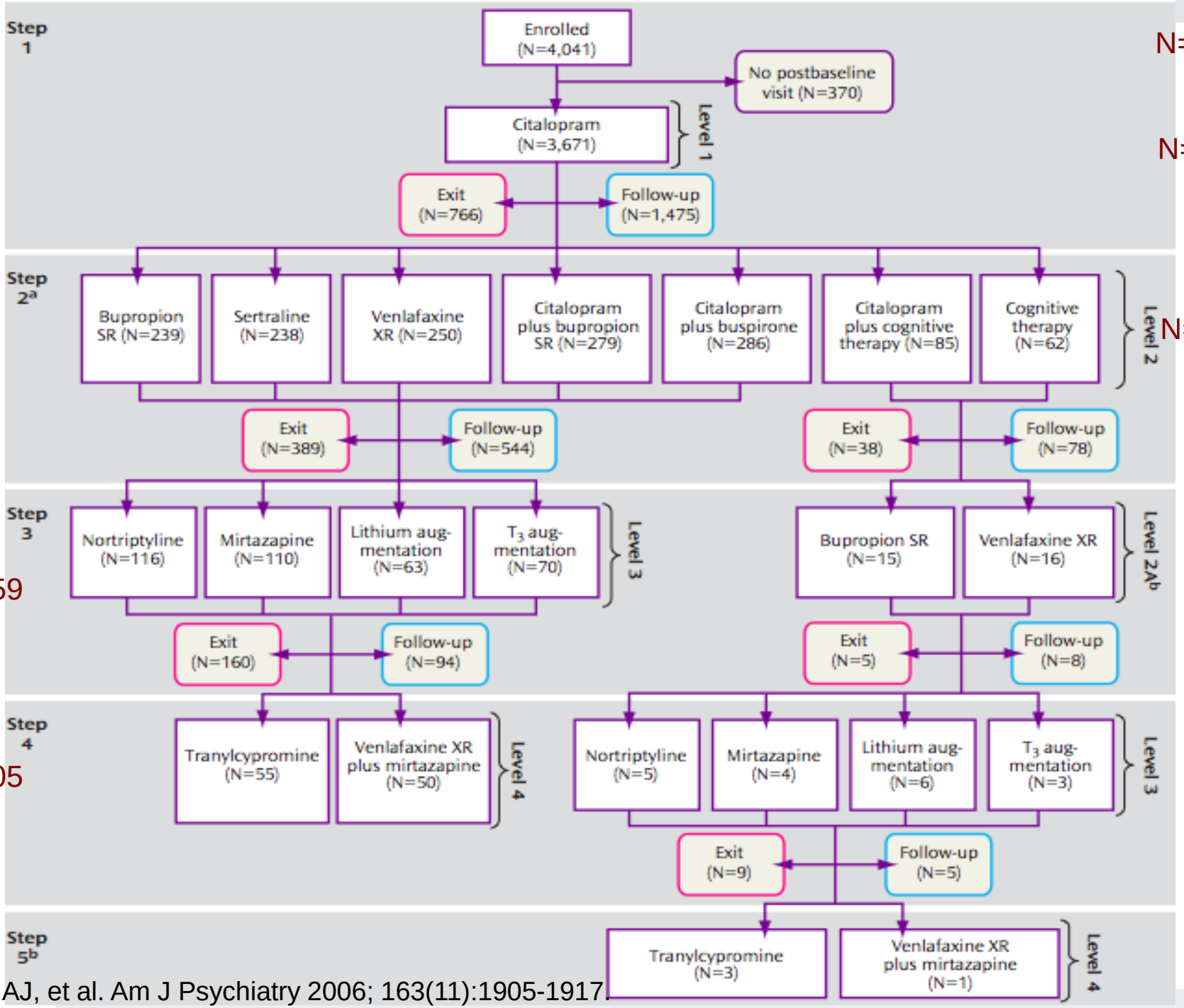
STEP →	1	2	3	4
N	3,671	1,439	390	123
AGE	41 years	42 years	44 years	46 years
FEMALE	62%	59%	51%	49%
ETHNICITY Caucasian African American Other	 76% 17% 7%	 77% 17% 6%	 80% 16% 5%	 82% 15% 2%
EDUCATION	13.5 years	13.4 years	13.1 years	13.1 years
EMPLOYED **UNEMPLOYED**	58% 36%	54% 41%	49% 45%	46% 47%
MARRIED	42%	40%	42%	46%
NO INSURANCE	34%	39%	39%	43%

Rush AJ, et al. Am J Psychiatry 2006;162:1905-1917.

POPULATION MDD HISTORY

STEP →	1	2	3	4
AGE 1st EPISODE	26 years	25 years	26 years	26 years
MDD DURATION	15 years	16.5 years	17 years	20 years
No. MDD Episode	5.9	6.8	7.3	8.3
RECURRENT MDD	75%	78%	75%	75%
PRIOR SUICIDE	17%	18%	19%	20%
PSYCH CARE	62%	63%	63%	62%
CURRENT EPISODE DURATION	25 months	28 months	32 months	42 months
HRSD-17	19.9	21	22.5	23.3
QIDS-SR-16	15.4	16.2	16.9	17.4

Rush AJ, et al. Am J Psychiatry 2006;162:1905-1917.



N=4041

N=3671

N=1439

N=359

N=31

N=105

N=18

N=4

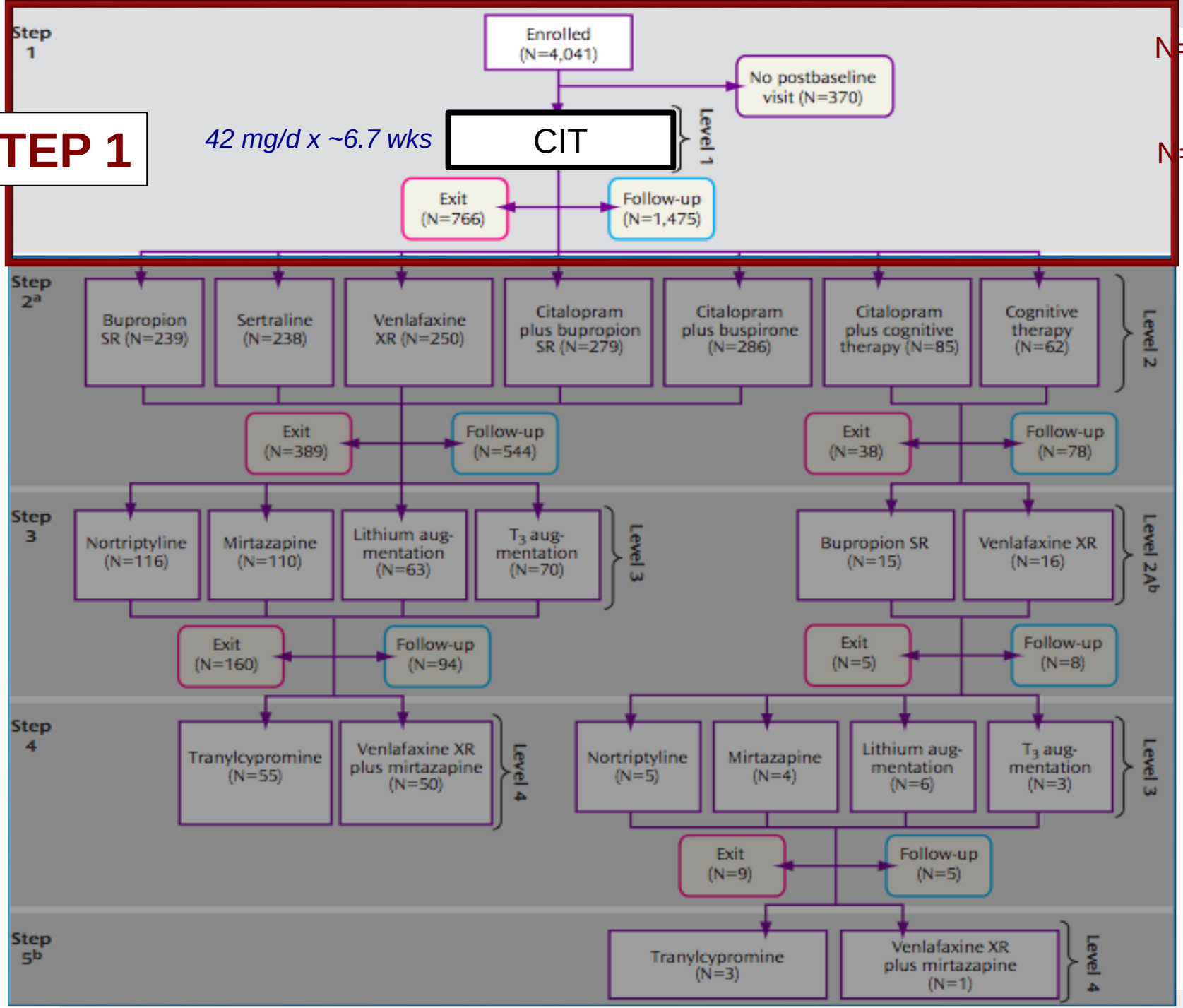
Rush AJ, et al. Am J Psychiatry 2006; 163(11):1905-1917.

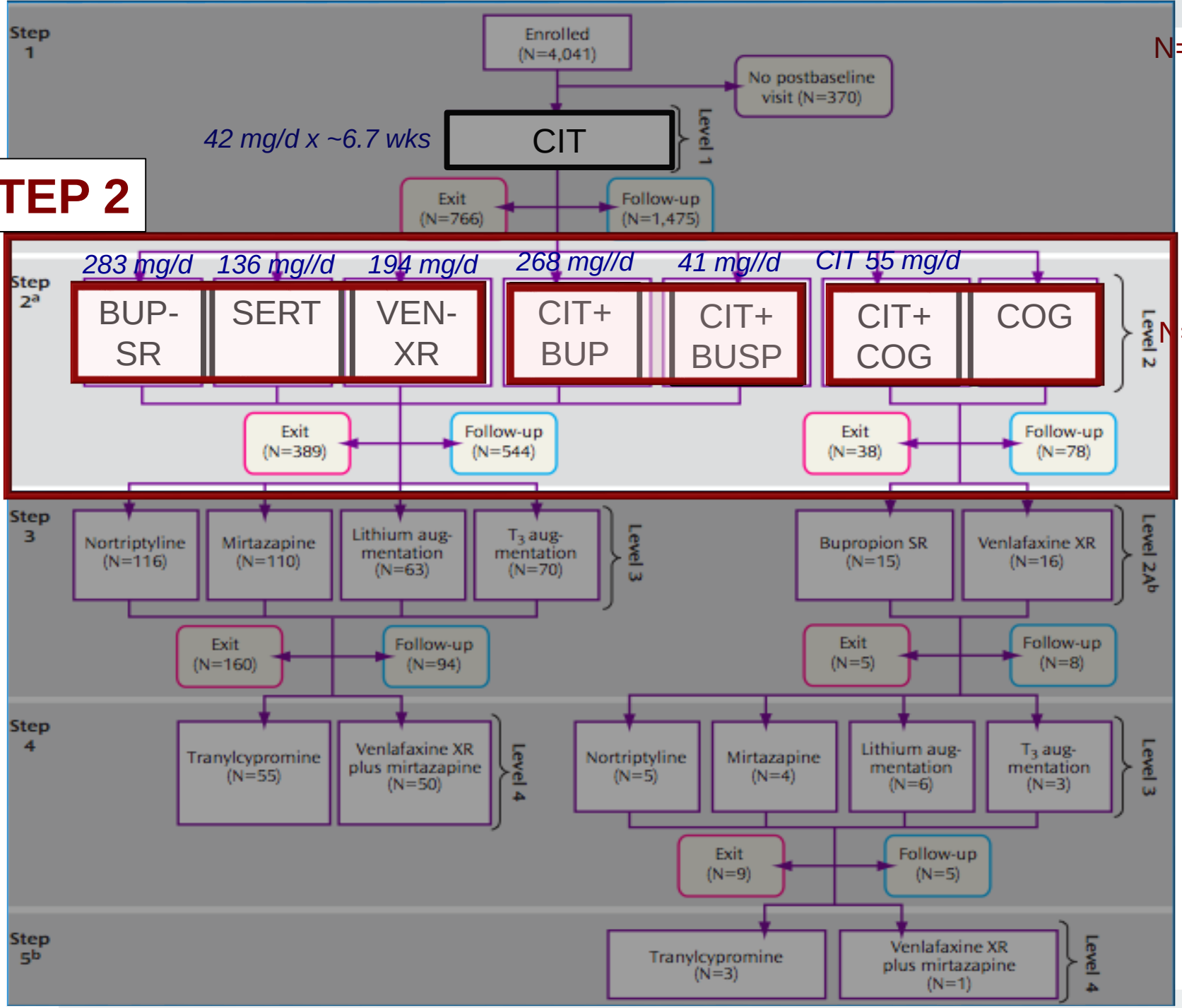
STEP 1

42 mg/d x ~6.7 wks

N=4041

N=3671

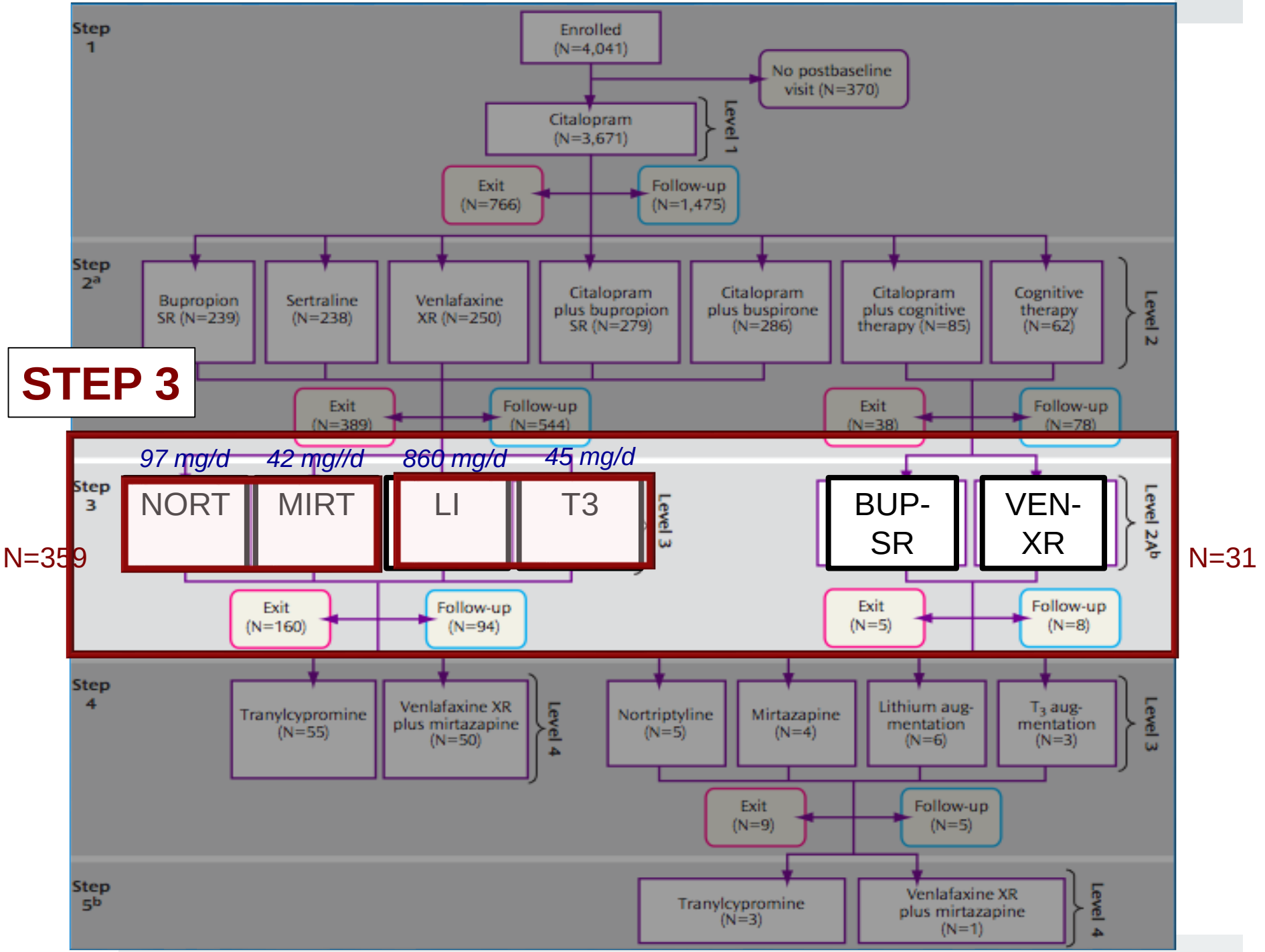


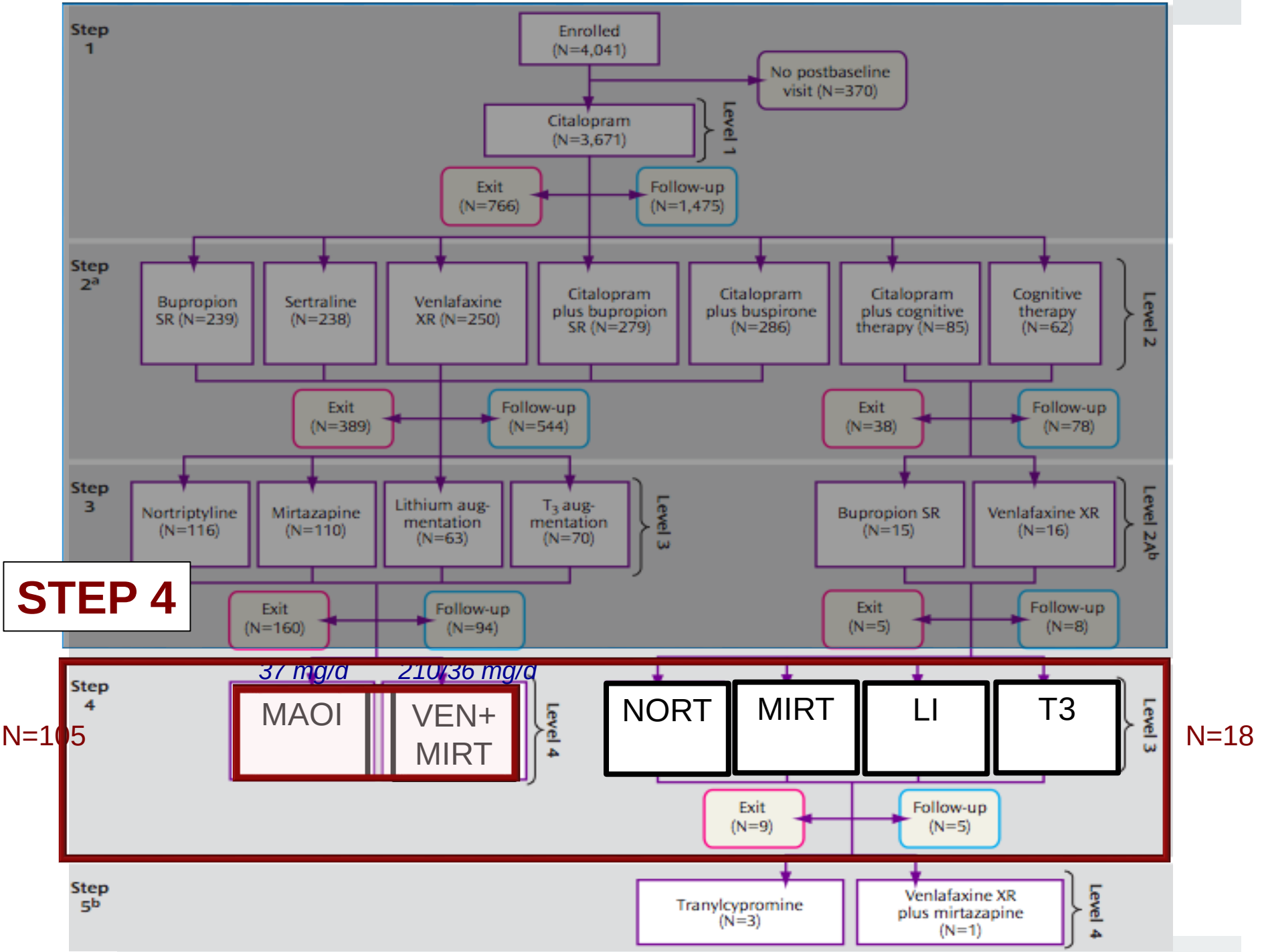


STEP 2

N=4041

N=1439


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 2a
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
STEP 3
Exit (N=389)
Follow-up (N=544)
Exit (N=38)
Follow-up (N=78)
97 mg/d
42 mg//d
860 mg/d
45 mg/d
Step 3
NORT
MIRT
LI
T3
Level 3
BUP-SR
VEN-XR
Level 2Ab
N=359
N=31
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)
T3 augmentation (N=3)
Level 3
Exit (N=9)
Follow-up (N=5)
Step 5b
Tranylcypromine (N=3)
Venlafaxine XR plus mirtazapine (N=1)
Level 4


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 2a
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Sertraline (N=238)
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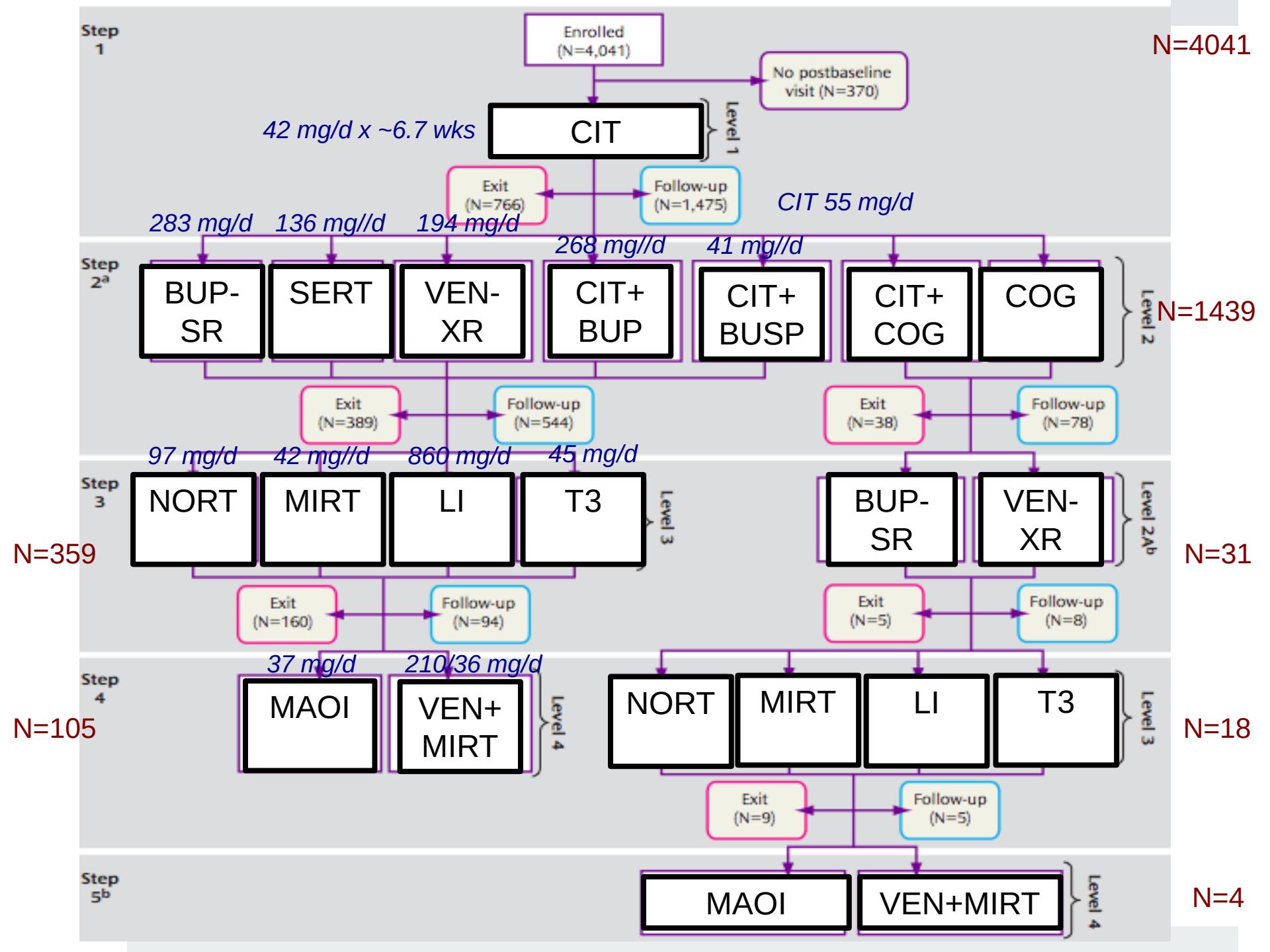
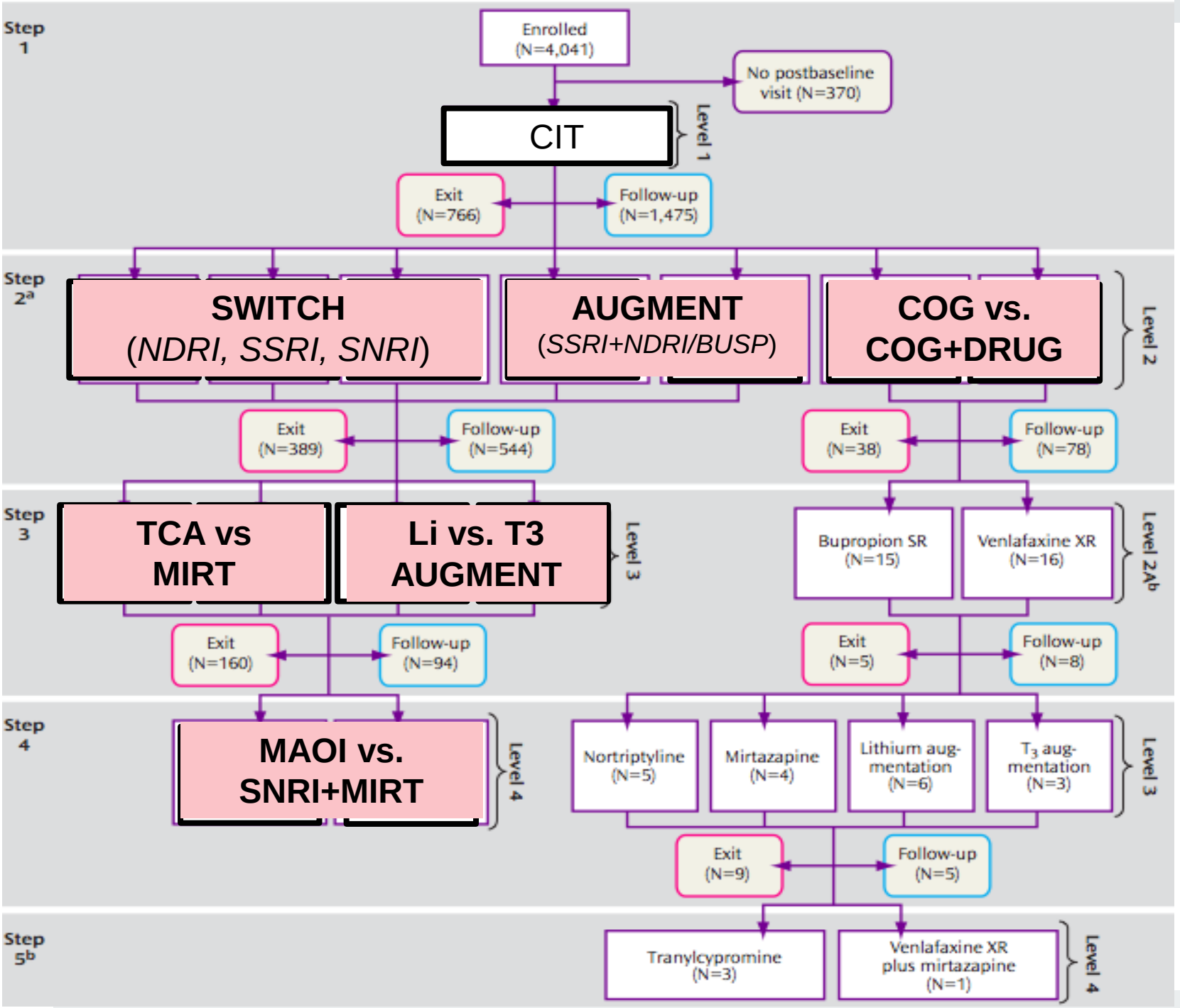
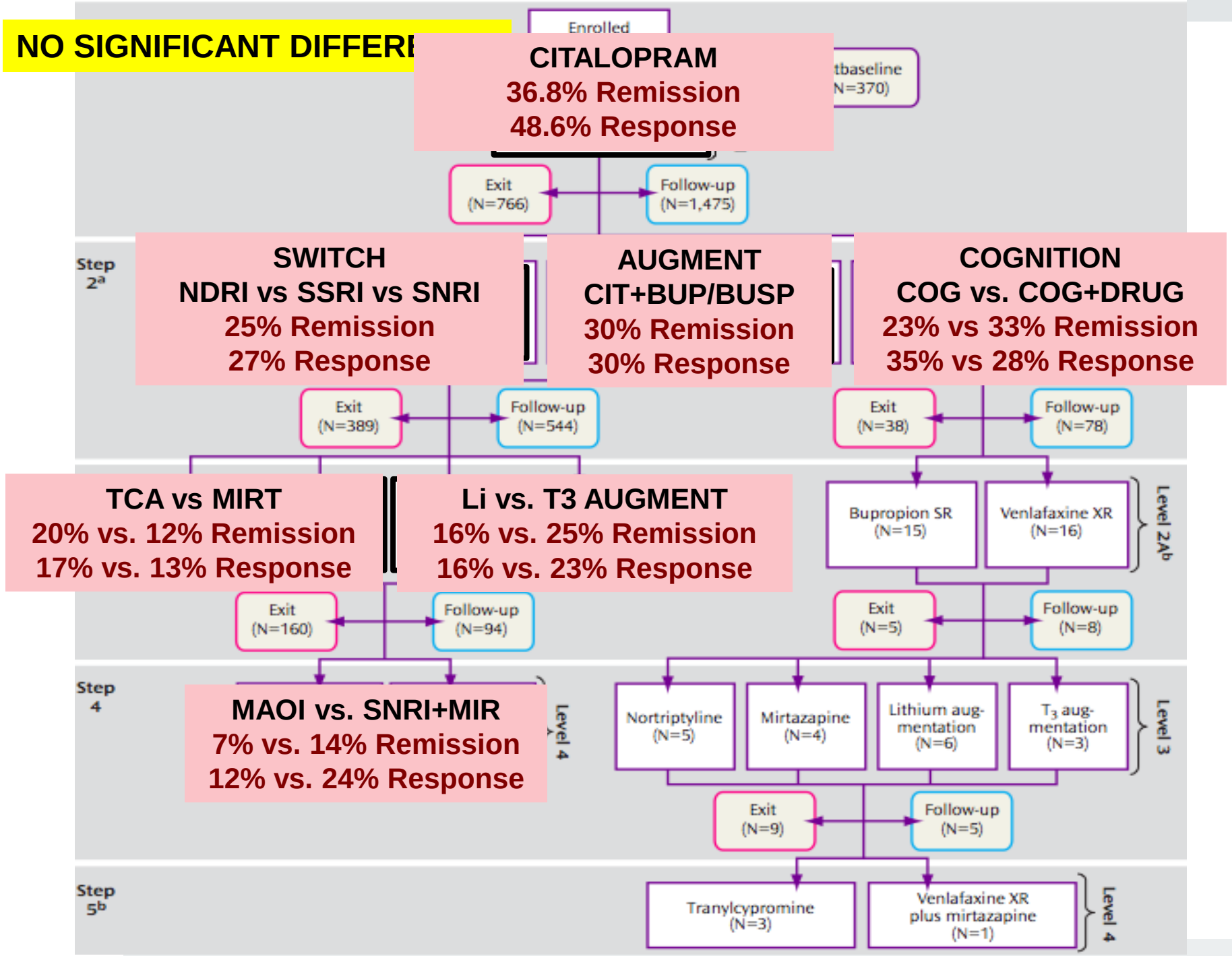
Citalopram plus bupropion SR (N=279)
Citalopram plus buspirone (N=286)
Citalopram plus cognitive therapy (N=85)
Cognitive therapy (N=62)
Level 2
Exit (N=389)
Follow-up (N=544)
Exit (N=38)
Follow-up (N=78)
Step 3
Nortriptyline (N=116)
Mirtazapine (N=110)
Lithium augmentation (N=63)
T3 augmentation (N=70)
Level 3
Bupropion SR (N=15)
Venlafaxine XR (N=16)
Level 2Ab
Exit (N=160)
Follow-up (N=94)
Exit (N=5)
Follow-up (N=8)
STEP 4
Step 4
37 mg/d
210/36 mg/d
MAOI
VEN+ MIRT
Level 4
N=105
NORT
MIRT
LI
T3
Level 3
N=18
Exit (N=9)
Follow-up (N=5)
Step 5b
Tranylcypromine (N=3)
Venlafaxine XR plus mirtazapine (N=1)
Level 4


Step 1
Enrolled (N=4,041)
N=4041
No postbaseline visit (N=370)
42 mg/d x ~6.7 wks
CIT
Level 1
Exit (N=766)
Follow-up (N=1,475)
CIT 55 mg/d
283 mg/d
136 mg//d
194 mg/d
268 mg//d
41 mg//d
Step 2a
BUP-SR
SERT
VEN-XR
CIT+BUP
CIT+BUSP
CIT+COG
COG
Level 2
N=1439
Exit (N=389)
Follow-up (N=544)
Exit (N=38)
Follow-up (N=78)
97 mg/d
42 mg//d
860 mg/d
45 mg/d
Step 3
NORT
MIRT
LI
T3
Level 3
N=359
BUP-SR
VEN-XR
Level 2Ab
N=31
Exit (N=160)
Follow-up (N=94)
Exit (N=5)
Follow-up (N=8)
37 mg/d
210/36 mg/d
Step 4
MAOI
VEN+MIRT
Level 4
N=105
NORT
MIRT
LI
T3
Level 3
N=18
Exit (N=9)
Follow-up (N=5)
Step 5b
MAOI
VEN+MIRT
Level 4
N=4


Step 1
Enrolled (N=4,041)
No postbaseline visit (N=370)
CIT
Level 1
Exit (N=766)
Follow-up (N=1,475)
Step 2a
SWITCH (NDRI, SSRI, SNRI)
AUGMENT (SSRI+NDRI/BUSP)
COG vs. COG+DRUG
Level 2
Exit (N=389)
Follow-up (N=544)
Exit (N=38)
Follow-up (N=78)
Step 3
TCA vs MIRT
Li vs. T3 AUGMENT
Level 3
Bupropion SR (N=15)
Venlafaxine XR (N=16)
Level 2Ab
Exit (N=160)
Follow-up (N=94)
Exit (N=5)
Follow-up (N=8)
Step 4
MAOI vs. SNRI+MIRT
Level 4
Nortriptyline (N=5)
Mirtazapine (N=4)
Lithium augmentation (N=6)
T3 augmentation (N=3)
Level 3
Exit (N=9)
Follow-up (N=5)
Step 5b
Tranylcypromine (N=3)
Venlafaxine XR plus mirtazapine (N=1)
Level 4


NO SIGNIFICANT DIFFERE
CITALOPRAM
36.8% Remission
48.6% Response
Enrolled
tbaseline
N=370)
Exit
(N=766)
Follow-up
(N=1,475)
Step
2a
SWITCH
NDRI vs SSRI vs SNRI
25% Remission
27% Response
AUGMENT
CIT+BUP/BUSP
30% Remission
30% Response
COGNITION
COG vs. COG+DRUG
23% vs 33% Remission
35% vs 28% Response
Exit
(N=389)
Follow-up
(N=544)
Exit
(N=38)
Follow-up
(N=78)
TCA vs MIRT
20% vs. 12% Remission
17% vs. 13% Response
Li vs. T3 AUGMENT
16% vs. 25% Remission
16% vs. 23% Response
Bupropion SR
(N=15)
Venlafaxine XR
(N=16)
Level 2Ab
Exit
(N=160)
Follow-up
(N=94)
Exit
(N=5)
Follow-up
(N=8)
Step
4
MAOI vs. SNRI+MIR
7% vs. 14% Remission
12% vs. 24% Response
Level 4
Nortriptyline
(N=5)
Mirtazapine
(N=4)
Lithium aug-
mentation
(N=6)
T3 aug-
mentation
(N=3)
Level 3
Exit
(N=9)
Follow-up
(N=5)
Step
5b
Tranylcypromine
(N=3)
Venlafaxine XR
plus mirtazapine
(N=1)
Level 4

STAR*D Take Home Points

- After initial treatment:
  - **<50%** will **respond**
  - Only **one-third** achieve **remission**

= lots of people will require treatment changes to reach therapeutic goals

- Remission rates decline with each subsequent treatment step as depression becomes more difficult to treat

Step 1: 37%
Step 2: 31%
Step 3: 14%
Step 4: 13%

- Important not to abandon a drug prematurely
  - Watchful waiting
  - May extend beyond 12 weeks

Response, mean **5.7 weeks**
Remission, mean **6.7 weeks**

40% of those who achieved remission did so **after 8 weeks**

STAR*D Unanswered Questions

- Lack of placebo control nor a group that continued citalopram
  - Cannot be certain that any treatment was specifically effective
  - Cannot exclude spontaneous remission
- Unblinded treatment delivery; basis for patient's choice not known
- Direct **comparison between different strategies** cannot be done
- **Optimal sequencing** of regimens not known
  - Should augmentation be used earlier to achieve greater remission rates sooner in more patients than with SSRIs alone?
- **Long-term risk-benefit** needs further study (sustained effects)
- Drugs with different mechanisms of action are roughly equivalent → depression pathophysiology (gene vs. environment)?

Studies

- *STAR*D 2006*
- **Zhou et al. 2015 Network Meta-Analysis**

What is the comparative efficacy, acceptability, and tolerability of various augmentation agents in adult patients with treatment-resistant depression?

- **Design**: Systematic review/network meta-analysis of RCTs (*active drug vs. active drug or placebo)*
- **Population:** Adults with **TRD** (Non-psychotic MDD + 1 past tx failure + failed ≥1 AD for current MDD episode)
- **Intervention:** 11 augmentation agents* for acute phase 6 wks
- **1^0 Outcome:** Response (≥50% ↓ on depression scale)
- **2^0 Outcome:** Remission (e.g., HAM-D ≤7)
- **Acceptability Outcome:** All-cause discontinuation (%)
- **Tolerability Outcome:** Side effects discontinuation (%)

Zhou X, et al. J Clin Psychiatry 2015; 76(4):e487-e498.

11 Augmentation Agents

Second Generation Antipsychotic	• Aripiprazole • Olanzapine • Quetiapine • Risperidone
Stimulant	• Methylphenidate
Thyroid Hormone	• T3 and/or T4
Antiepileptic	• Lamotrigine
Lithium	• Lithium
Beta-blocker	• Pindolol
Azapirone Anxiolytic	• Buspirone
Antidepressant (NDRI)	• Bupropion

Excluded: sex hormone tx

Missing: divalproex, carbamazepine, ziprasidone, dopamine agonist, modafinil

Zhou X, et al. J Clin Psychiatry 2015; 76(4):e487-e498.

Study and Patient Characteristics

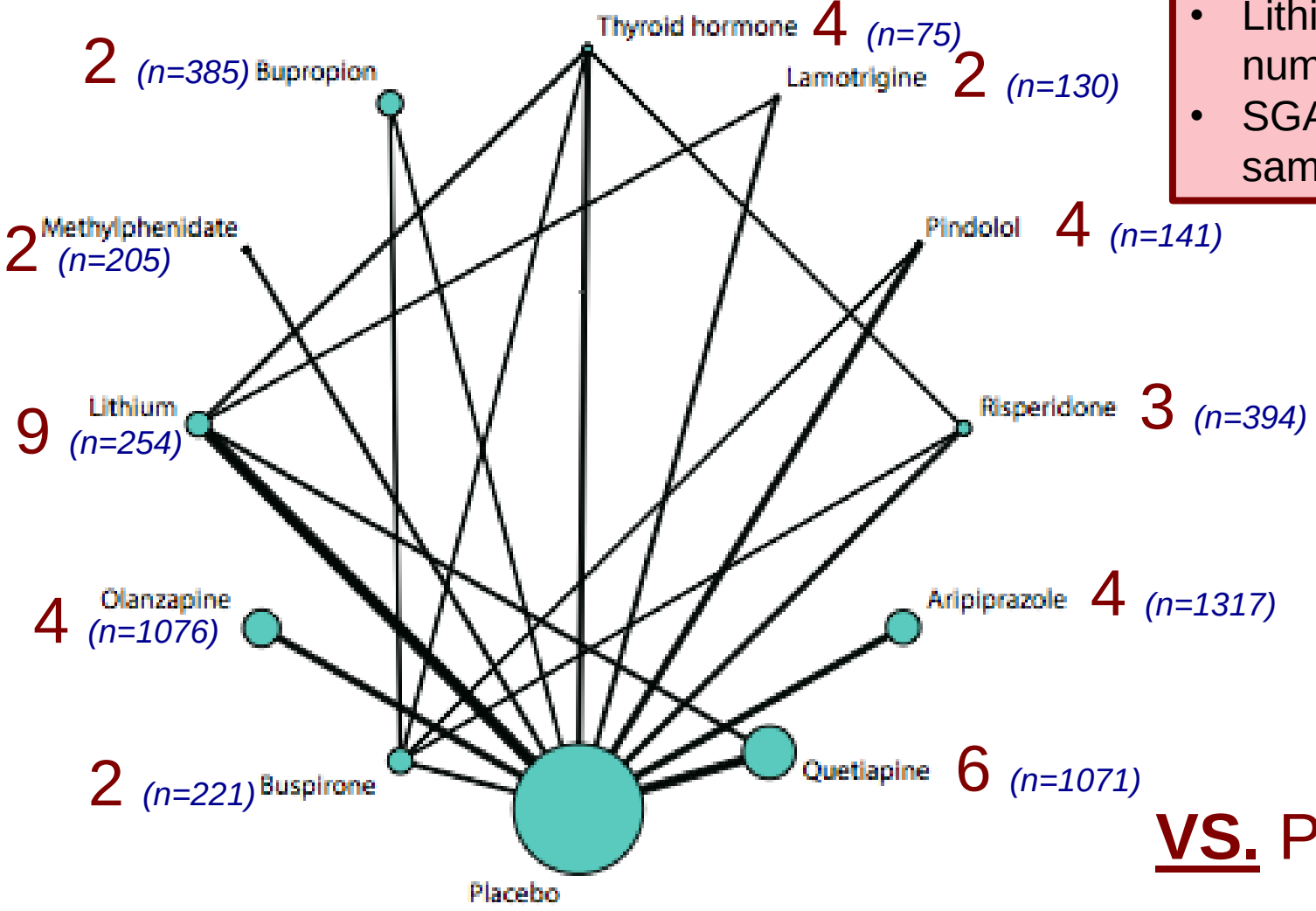
STUDY	
No. of Trials	48
Publication years	1978-2012
Mean (range) **N per group**	67.8 (4-286)
Mean (range) **study duration**	6.2 weeks (1-14 weeks)
Overall study quality	“Good”

PATIENT	
N	6,654
MEAN AGE	43.8 years
Age ≤65 Years	65.6%
FEMALE	64.9%
TRD STAGE: ≥I ≥II ≥III	35 RCTs 12 RCTs 1 RCT
MEAN SCORE HDRS-17 HDRS-21 HDRS-25 MADRS	 21.16 20.30 28.21 27.97

Zhou X, et al. J Clin Psychiatry 2015; 76(4):e487-e498.

Network Plot for Primary Efficacy

- Lithium had highest number of studies
- SGAs had higher sample size



[a]Line width is proportional to the number of trials comparing each treatment pair. Nodal size is proportional to the number of randomized participants (sample size).

VS. PLACEBO

Zhou X, et al. J Clin Psychiatry 2015; 76(4):e487-e498.

Primary Outcome

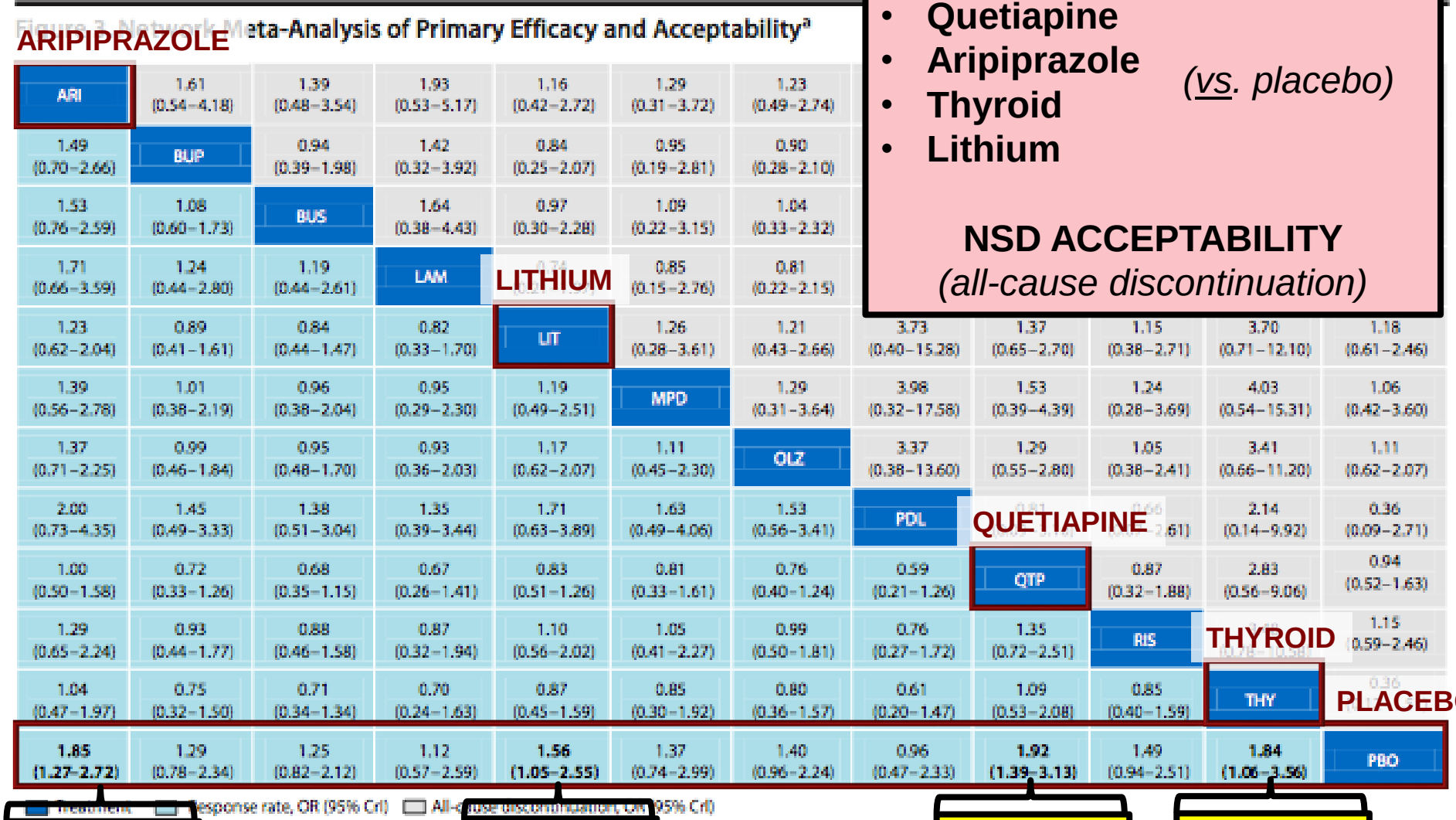
SS RESPONSE RATE for:

- **Quetiapine**
- **Aripiprazole**
- **Thyroid**
- **Lithium**

(vs. placebo)

NSD ACCEPTABILITY

(all-cause discontinuation)



1.85 (1.27-2.72)

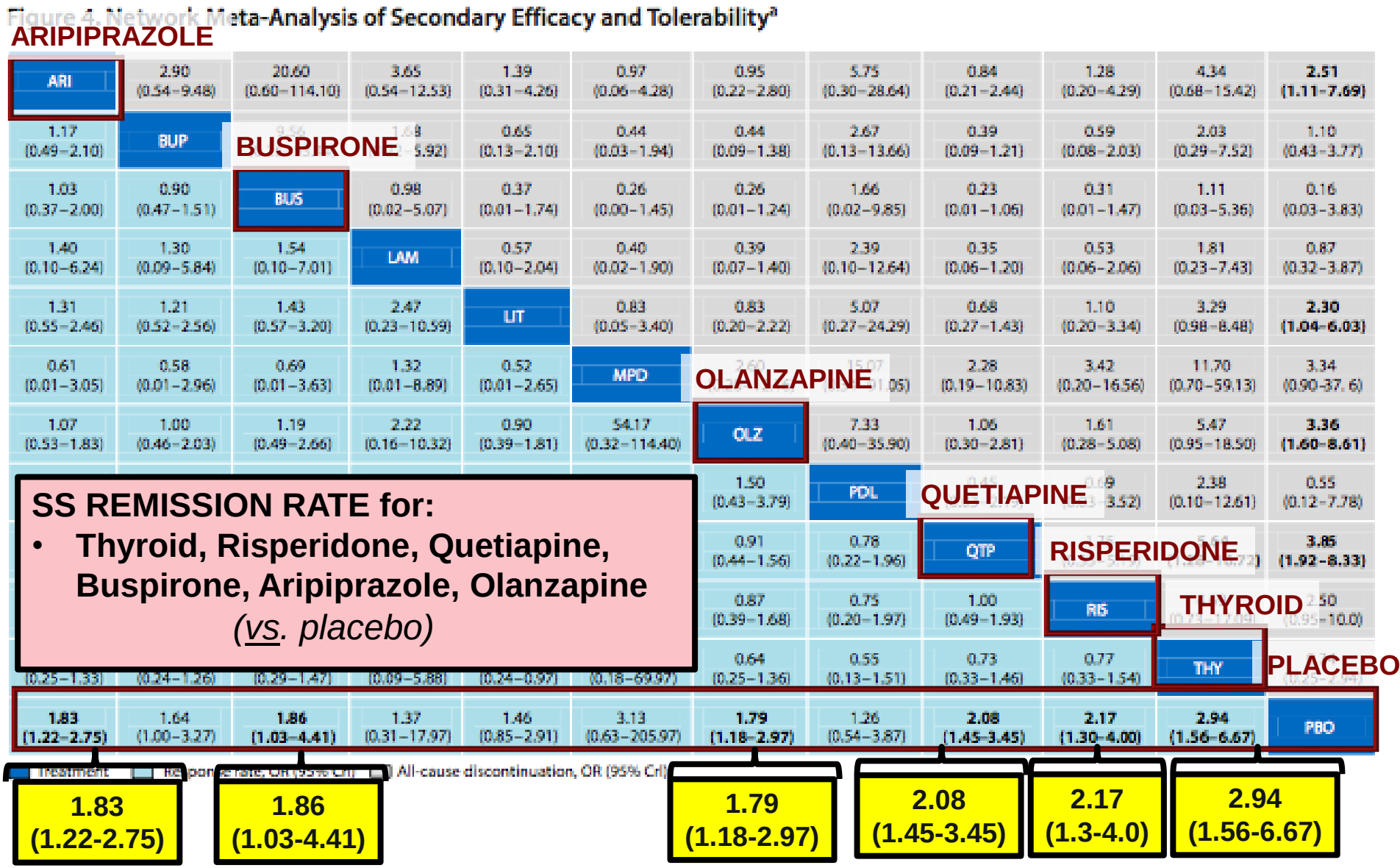
1.56 (1.05-2.55)

1.92 (1.39-3.13)

1.84 (1.06-3.56)

Zhou X, et al. J Clin Psychiatry 2015; 76(4):e487-e498.

Secondary Outcome

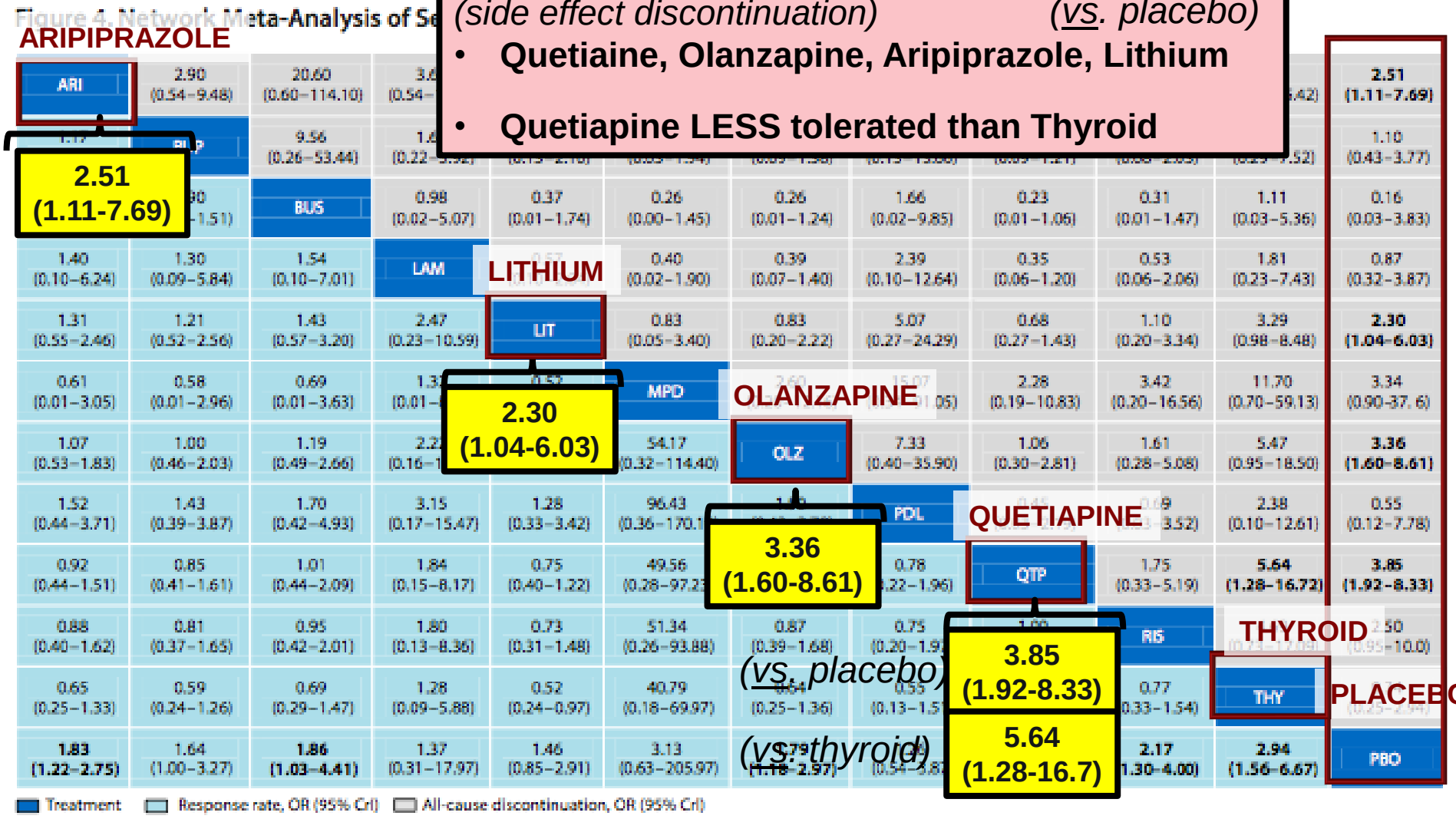


Zhou X, et al. J Clin Psychiatry 2015; 76(4):e487-e498.

Secondary Outcome

SS TOLERABILITY for:
(side effect discontinuation) *(vs. placebo)*

- **Quetiaine, Olanzapine, Aripiprazole, Lithium**
- **Quetiapine LESS tolerated than Thyroid**



Zhou X, et al. J Clin Psychiatry 2015; 76(4):e487-e498.

Sensitivity Analysis

- Stronger primary efficacy estimates for **aripiprazole and quetiapine** than for ***thyroid hormone and lithium***
- Lithium had beneficial effects with non-TCA but not with TCA (small N)

VARIABLES:

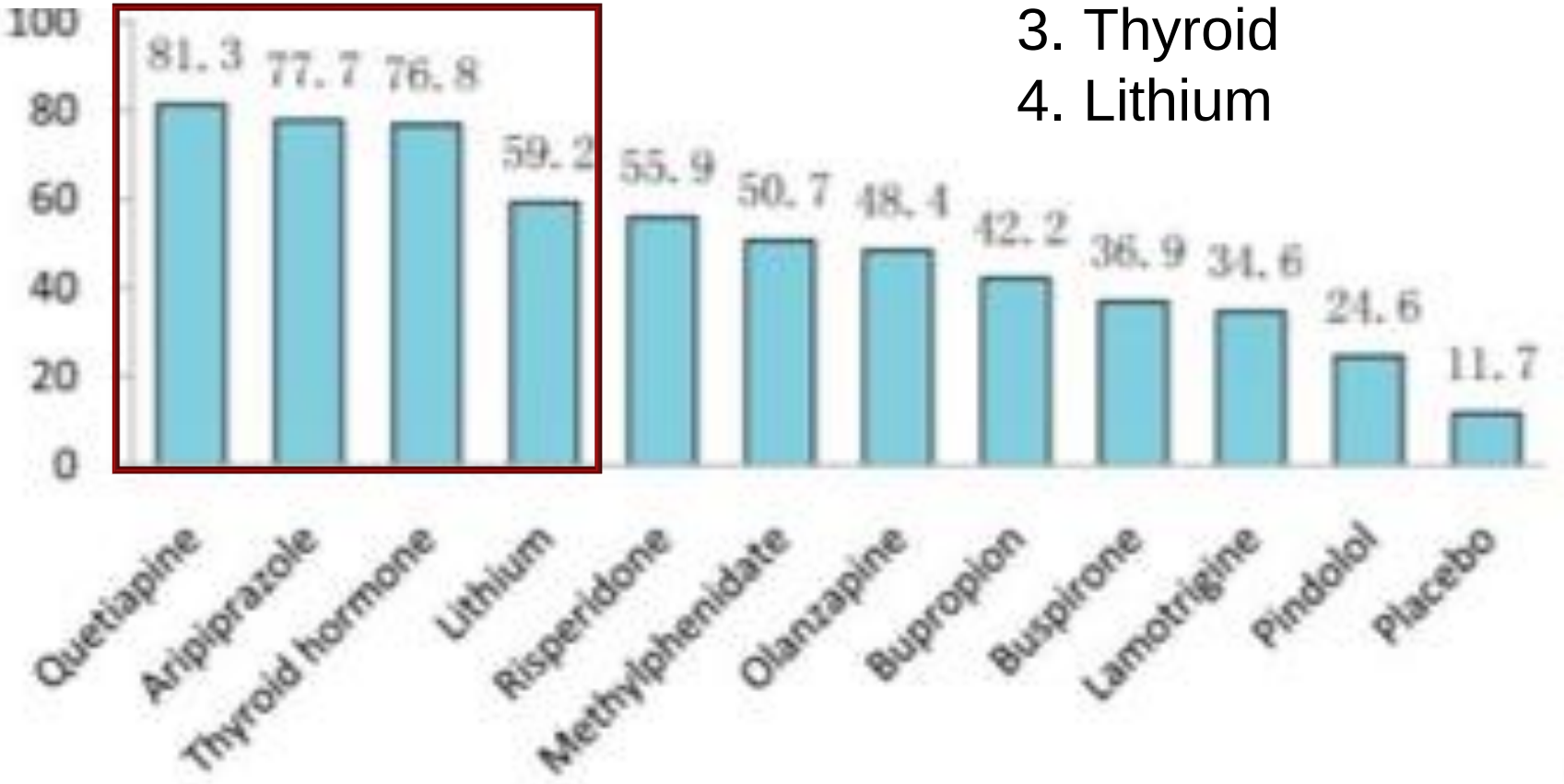
- Therapeutic dose
- Acute treatment duration (4-12 wks)
- No imputation method
- No bipolar patients
- Blinded design
- Refractory duration (≥4 wks)
- Study time (no RCTs pre-2004)
- Without sponsorship
- Non-TCA

Zhou X, et al. J Clin Psychiatry 2015; 76(4):e487-e498.

Ranking of Efficacy

Response

1. Quetiapine
2. Aripiprazole
3. Thyroid
4. Lithium



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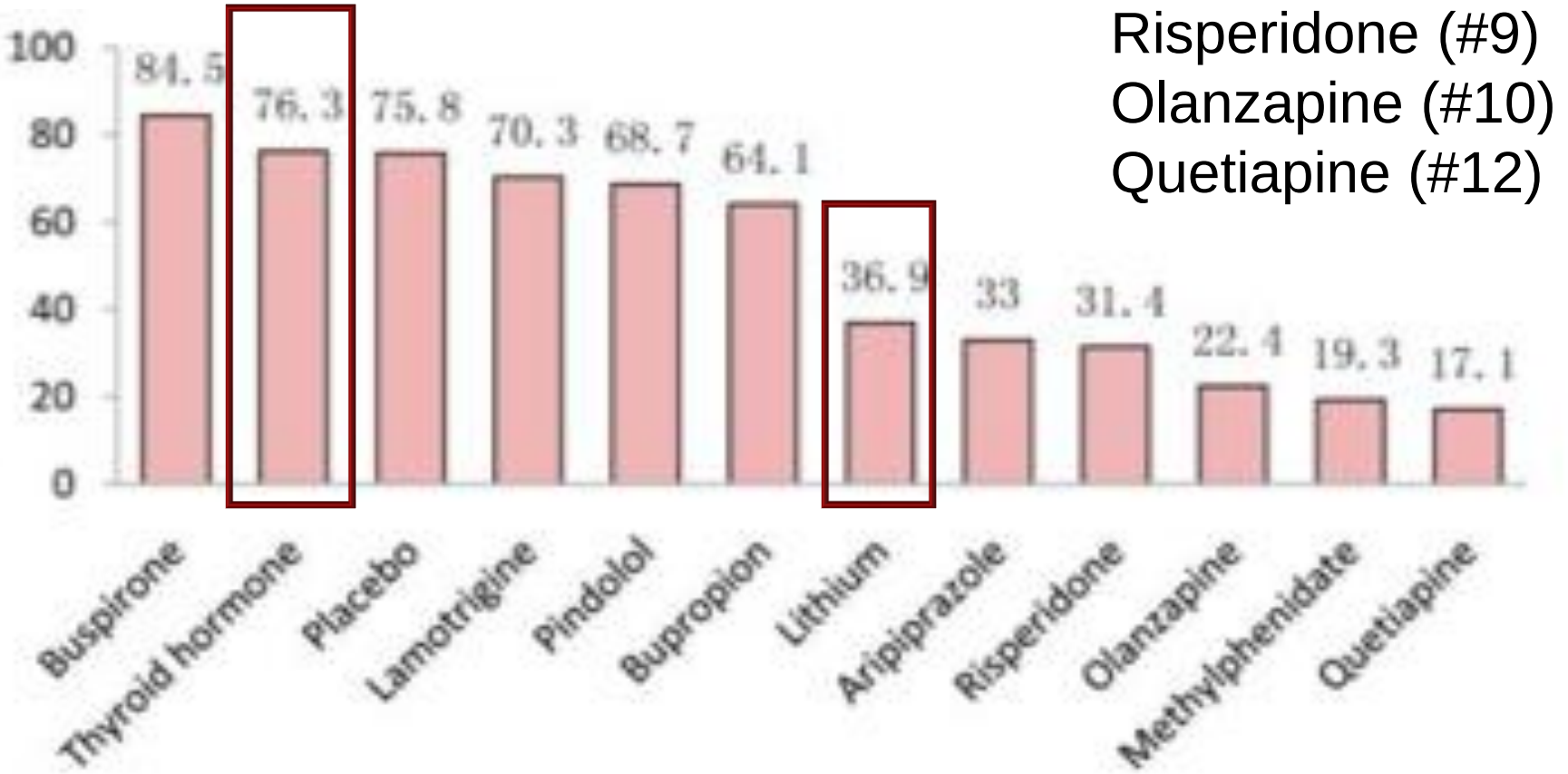
Ranking of Tolerability

Tolerability



Thyroid (#2)
Lithium (#7)
Aripiprazole (#8)
Risperidone (#9)
Olanzapine (#10)
Quetiapine (#12)

Zhou X, et al. J Clin Psychiatry 2015; 76(4):e487-e498.

Quetiapine and aripiprazole had the most robust evidence for augmentation therapy in terms of efficacy, acceptability, and tolerability in ad

OR (response):
- QUE 1.92
- ARIP 1.85
- T3/T4 1.84
- Li 1.56

OR (D/C SE):
- QUE 3.85
- ARIP 2.51
- **T3/T4 1.36**
- Li 2.30

A few things to consider:

- **Thyroid hormone and lithium** may be better tolerated
- Half the lithium and thyroid hormone trials were **small** (n≤30) and **brief** (≤3 weeks) vs. quetiapine/aripiprazole trials were large (n≥100) with longer follow-up (6-12 weeks)
- Choice of dose and duration (dose-related SE, sustained effects)
- Duration of diagnosis and previous therapies (number of trials, nonresponse vs. partial response) not known
- Some effect moderators not measured (original patient data)
- Industry influence

NMA Take Home Points

- The results discourage:
  - Buspirone, bupropion, methylphenidate, lamotrigine, and pindolol augmentation (no better than placebo)
  - Olanzapine, risperidone (aripiprazole, quetiapine better efficacy results)
- The results favor
  - Aripiprazole or quetiapine for 6-12 weeks, but the risk of discontinuation due to adverse effects is 2-4 times higher than placebo
  - 3-4-week trial of T3/T4 or lithium seems to provide the quickest option (but long-term unknown)

Summary

- Remission difficult to achieve with each failed trial
- Direct comparison of strategies limited (especially longer term effects on preventing relapse and recurrence)
- Which and when to employ a specific strategy to any specific patient

CASE

- **43 year-old female** with moderate to severe **depression** (12 years)
- Trialed monotherapy:
  - Citalopram (6 months – no response)
  - Paroxetine (1 month – side effects)
  - Venlafaxine XR (8 months – minimal response)

CASE

Which of the following would you recommend next?

A. Combination venlafaxine XR plus mirtazapine

B. Switch to fluoxetine

C. Switch to bupropion SR

D. Augment with thyroid hormone

E. Augment with aripiprazole

Clinical Considerations in TRD

- The pressures to prescribe
- Side effect burden
- More More More
- Diagnostic factors
- Consultation

The pressure to prescribe

- Busy clinic settings with limited time per patient
- Industry influence
  - Physician detailing influences physician prescribing, especially in clinical practices with only a few GPs
  - Prevalence ratio of depression to schizophrenia is **20:1**, yet in 2005 promotional expenditures were **2:1**
- Patient demands for a ‘quick fix’
  - Vs. psychotherapy
- Lack of access to alternative treatment options
  - Psychotherapy, rTMS, ECT

Donohue JM et al. *NEJM* 2007

Side effect burden

- Quetiapine (and other SGA's)
  - Metabolic side effects
    - Associated with a 3-fold increased risk of Type II Diabetes
    - Onset within the first year of use
    - Risk remains elevated for up to 1 year following d/c
  - Are we obtaining proper informed?
    - Weight gain, lipid abnormalities, tardive dyskinesia, etc.

Bobo WA et al. *JAMA Psychiatry* 2013

More More More

- The need for regular reassessment of a medication regimen
  - When a medication does not work, the tendency is to add another without removing an existing medication
  - Patients often are prescribed multiple medications from the same class
- Medications are often switched/added too early
  - Dose not optimized/maximized
  - Inadequate trial duration
  - Need for proper psychoeducation about expectations and side effect anticipation

Diagnostic factors

- What is TRD exactly?
  - Prevalence of mood and anxiety disorders in MB is 20%
  - Depression represents a heterogeneous group of disorders

- Diagnostic reassessment
  - Is your TRD patient actually suffering from
    - Personality disorder
    - Alcohol or drug use disorder
    - Adjustment disorder

Consultation

- Early consultation with psychiatry
- Rapid Access to Consultative Expertise (RACE)
  - (Close to) Real-time consultation with a psychiatrist
  - Available to all GP’s in MB

Thank you!