# What Really Works in Treatment Resistant Depression?

Daniel Zigman, MD, FRCPC

# Disclosures

- I have received honorarium from Aifred, an AI company for participating in a clinical trial
  - There is no relationship with this session

- I will be discussing off-label treatments

# Objectives

- Define and recognize TRD
- Understand advantages and disadvantages of therapies that have proven beneficial in TRD
- Understand the role of esketamine, second generation antipsychotics, lithium and other options

# Overview

- Initial treatment of depression (CANMAT guidelines)
- Next step strategies
- Treatment resistant depression
- Treatment refractory depression


*"Would the gentleman prefer an antidepressant?"*

# Poll

- A 35 year old business woman presents with a first depressive episode for the past 2 months in context of problems in family and stress at work
  - Depressed mood, crying daily, insomnia, decreased appetite, anxiety, impaired concentration, death wishes, -ve rumination
  - No substance use, psychiatric or medical comorbidity
  - Significant functional impairment, unable to work

- Which of the following treatment options would you chose?
  - A) SSRI
  - B) SNRI
  - C) Bupropion
  - D) Mirtazapine
  - E) CBT

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# Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments

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# CANMAT 2016 guidelines

| Antidepressant (Brand Name(s)) | Mechanism | Dose Range |
|---|---|---|
| **First line (Level 1 Evidence)** | | |
| Agomelatine[a] (Valdoxan) | $MT_1$ and $MT_2$ agonist; 5-$HT_2$ antagonist | 25-50 mg |
| Bupropion (Wellbutrin)[b] | NDRI | 150-300 mg |
| Citalopram (Celexa, Cipramil) | SSRI | 20-40 mg |
| Desvenlafaxine (Pristiq) | SNRI | 50-100 mg |
| Duloxetine (Cymbalta) | SNRI | 60 mg |
| Escitalopram (Cipralex, Lexapro) | SSRI | 10-20 mg |
| Fluoxetine (Prozac) | SSRI | 20-60 mg |
| Fluvoxamine (Luvox) | SSRI | 100-300 mg |
| Mianserin[a] (Tolvon) | $\alpha_2$-Adrenergic agonist; 5-$HT_2$ antagonist | 60-120 mg |
| Milnacipran[a] (Ixel) | SNRI | 100 mg |
| Mirtazapine (Remeron)[c] | $\alpha_2$-Adrenergic agonist; 5-$HT_2$ antagonist | 15-45 mg |
| Paroxetine (Paxil)[d] | SSRI | 20-50 mg<br>25-62.5 mg for CR version |
| Sertraline (Zoloft) | SSRI | 50-200 mg |
| Venlafaxine (Effexor)[e] | SNRI | 75-225 mg |
| Vortioxetine (Brintellix, Trintellix)[f] | Serotonin reuptake inhibitor; 5-$HT_{1A}$ agonist; 5-$HT_{1B}$ partial agonist; 5-$HT_{1D}$, 5-$HT_{3A}$, and 5-$HT_7$ antagonist | 10-20 mg |
| **Second line (Level 1 Evidence)** | | |
| Amitriptyline, clomipramine, and others | TCA | Various |
| Levomilnacipran (Fetzima)[f] | SNRI | 40-120 mg |
| Moclobemide (Manerix) | Reversible inhibitor of MAO-A | 300-600 mg |
| Quetiapine (Seroquel)[e] | Atypical antipsychotic | 150-300 mg |
| Selegiline transdermal[a] (Emsam) | Irreversible MAO-B inhibitor | 6-12 mg daily transdermal |
| Trazodone (Desyrel) | Serotonin reuptake inhibitor; 5-$HT_2$ antagonist | 150-300 mg |
| Vilazodone (Viibryd)[f] | Serotonin reuptake inhibitor; 5-$HT_{1A}$ partial agonist | 20-40 mg (titrate from 10 mg) |
| **Third line (Level 1 Evidence)** | | |
| Phenelzine (Nardil) | Irreversible MAO inhibitor | 45-90 mg |
| Tranylcypromine (Parnate) | | 20-60 mg |
| Reboxetine[a] (Edronax) | Noradrenaline reuptake inhibitor | 8-10 mg |

Kennedy, Can J Psychiatry, 2016

# CANMAT 2016 guidelines

**Table 5.** Recommendations for Clinical Specifiers and Dimensions of Major Depressive Disorder.

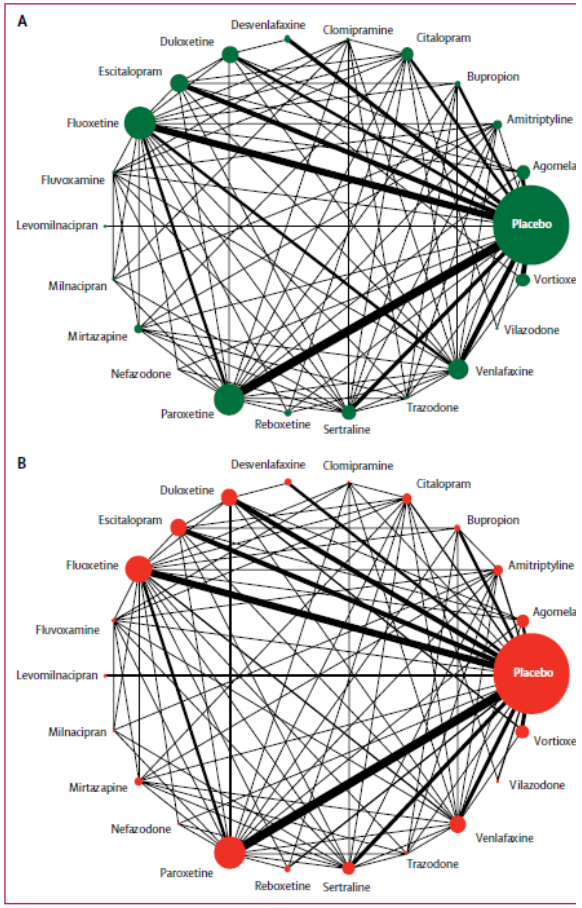
| Specifiers/ Dimensions | Recommendations (Level of Evidence) | Comments |
|---|---|---|
| With anxious distress[a] | • Use an antidepressant with efficacy in generalized anxiety disorder (Level 4) | • No differences in efficacy between SSRIs, SNRIs, and bupropion (Level 2) |
| With catatonic features[a] | • Benzodiazepines (Level 3) | • No antidepressants have been studied |
| With melancholic features[a] | • No specific antidepressants have demonstrated superiority (Level 2) | • TCAs and SNRIs have been studied |
| With atypical features[a] | • No specific antidepressants have demonstrated superiority (Level 2) | • Older studies found MAO inhibitors superior to TCAs |
| With psychotic features[a] | • Use antipsychotic and antidepressant cotreatment (Level 1) | • Few studies involved atypical antipsychotics |
| With mixed features[a] | • Lurasidone[b] (Level 2)<br>• Ziprasidone[b] (Level 3) | • No comparative studies |
| With seasonal pattern[a] | • No specific antidepressants have demonstrated superiority (Level 2 and 3) | • SSRIs, agomelatine, bupropion, and moclobemide have been studied |
| With cognitive dysfunction | • Vortioxetine (Level 1)<br>• Bupropion (Level 2)<br>• Duloxetine (Level 2)<br>• SSRIs (Level 2)[b]<br>• Moclobemide (Level 3) | • Limited data available on cognitive effects of other antidepressants and on comparative differences in efficacy |
| With sleep disturbances | • Agomelatine (Level 1)<br>• Mirtazapine (Level 2)<br>• Quetiapine (Level 2)<br>• Trazodone (Level 2) | • Beneficial effects on sleep must be balanced against potential for side effects (e.g., daytime sedation) |
| With somatic symptoms | • Duloxetine (pain) (Level 1)<br>• Other SNRIs (pain) (Level 2)<br>• Bupropion (fatigue) (Level 1)<br>• SSRIs[b] (fatigue) (Level 2)<br>• Duloxetine[b] (energy) (Level 2) | • Few antidepressants have been studied for somatic symptoms other than pain<br>• Few comparative antidepressant studies for pain and other somatic symptoms |

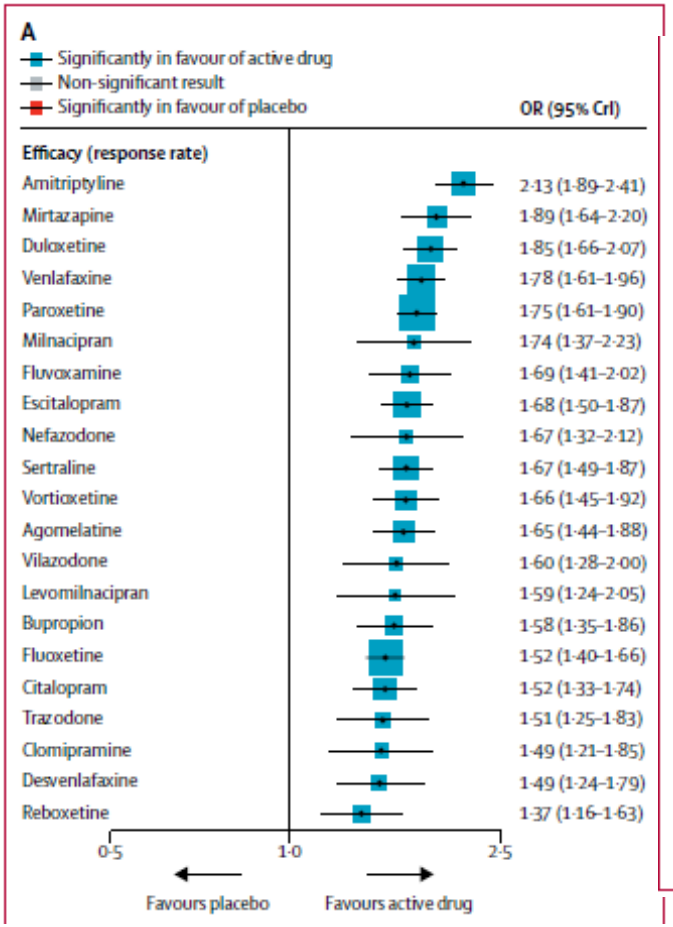
MAO, monoamine oxidase; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a]*DSM-5* specifiers.
[b]Comparisons only with placebo.

Kennedy, Can J Psychiatry, 2016

# 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

*Andrea Cipriani, Toshi A Furukawa*, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes*



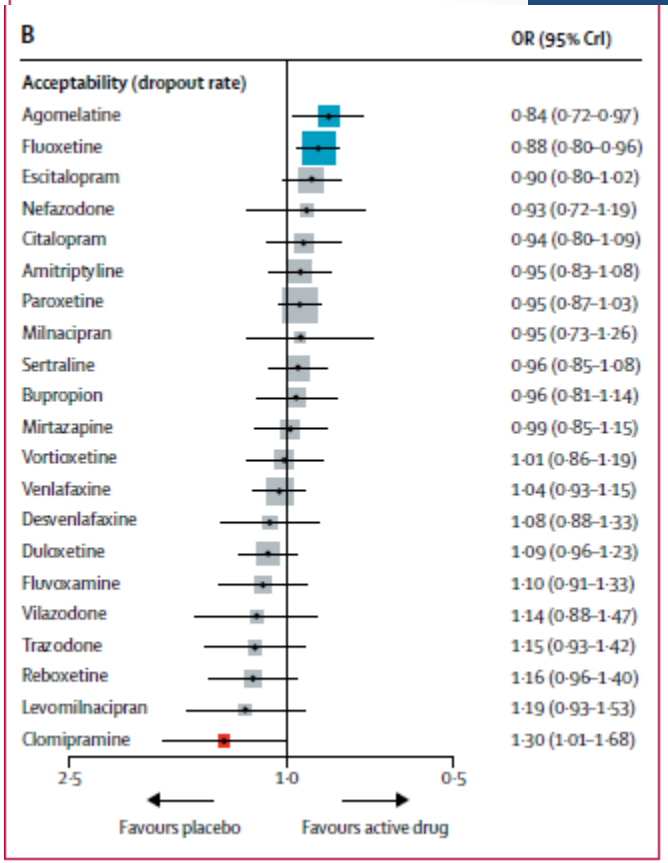




***Figure 2:*** **Network meta-analysis of eligible comparisons for efficacy (A) and acceptability (B)**
Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (ie, sample size).

# Poll

- A 35 year old business woman presents with a first depressive episode for the past 4 months
  - Depressed mood, crying daily, insomnia, decreased appetite, anxiety, impaired concentration, death wishes, -ve rumination
  - Tried sertraline 50 mg x 4 wk then increased to 100 mg x4 wk
  - No improvement

- Which of the following treatment options would you chose?
  - A) Switch to 2nd SSRI
  - B) Switch to SNRI
  - C) Add mirtazapine
  - D) Add aripiprazole
  - E) Switch to CBT


*"Of course you feel great. These things are loaded with antidepressants."*

# Switching vs. Augmenting

**Table 12.** Factors to Consider in Choosing between Switching to Another Antidepressant Monotherapy or Adding an Adjunctive Medication (Level 3 Evidence).

Consider switching to another antidepressant when:

- It is the first antidepressant trial.
- There are poorly tolerated side effects to the initial antidepressant.
- There is no response (<25% improvement) to the initial antidepressant.[a]
- There is more time to wait for a response (less severe, less functional impairment).
- Patient prefers to switch to another antidepressant.

Consider an adjunctive medication when:

- There have been 2 or more antidepressant trials.
- The initial antidepressant is well tolerated.
- There is partial response (>25% improvement) to the initial antidepressant.
- There are specific residual symptoms or side effects to the initial antidepressant that can be targeted.
- There is less time to wait for a response (more severe, more functional impairment).
- Patient prefers to add on another medication.

[a]For the initial antidepressant trial. In subsequent trials, lack of response (<25% improvement) may not be a factor for choosing between switch and adjunctive strategies.

Kennedy, Can J Psychiatry, 2016

# Limited evidence to support switching

**Table 1. Characteristics of Studies Included In a Systematic Meta-Analysis Comparing Switching to a New Antidepressant Versus Continuation of the Initial Antidepressant in Patients With Major Depressive Disorder After Nonresponse to Antidepressant Monotherapy**

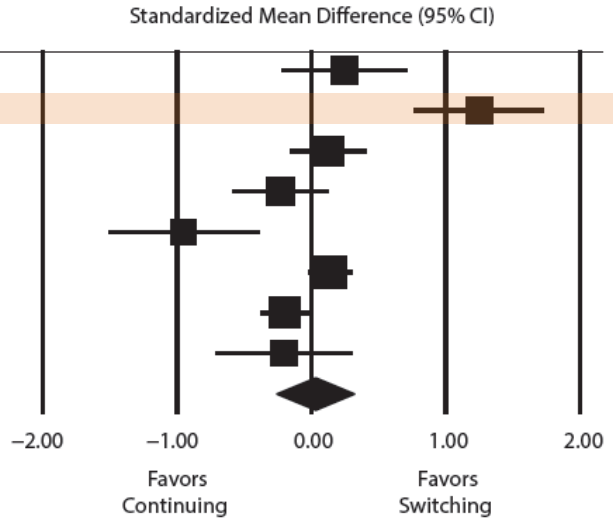
| Study/First Author | Year of Publication | Initial and Continuation Antidepressant | Switch Antidepressant | Follow-Up Time (wk) | N After Randomization[a] | Dose Escalation Allowed in the Continuation Arm? | Low Risk of Bias According to Cochrane Collaboration Tool for Assessing Risk of Bias? |
|---|---|---|---|---|---|---|---|
| Ferreri[28] | 2001 | Fluoxetine | Mianserin | 6 | 71 | No | Yes |
| Corya[29] | 2006 | Venlafaxine | Fluoxetine | 12 | 119 | No | No |
| Souery[27] | 2011 | Desipramine or citalopram | Desipramine or citalopram | 4 | 59 | No | Yes |
| Shelton[30] | 2005 | Nortriptyline | Fluoxetine | 8 | 210 | No | No |
| Romera[32] | 2012 | Escitalopram | Duloxetine | 4 | 566 | Yes | Yes |
| Bose[33] | 2012 | Escitalopram | Duloxetine | 8 | 472 | Yes | Yes |
| Petrescu[34] | 2014[b] | Any SSRI | Duloxetine | 8 | 52 | Yes | No |
| Zhu[31] | 2003 | Various SSRIs | Mirtazapine | 6 | 78 | Yes | No |

[a]A total of 1,627 patients were included in the meta-analysis.
[b]Published as abstract only.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

?? MRT, BUP, VORT could be exceptions

**A. Standardized Mean Differences**

| Study/First Author | Standardized Mean Difference | Standard Error | Variance | Lower Limit | Upper Limit | *Z* Value | *P* Value |
|---|---|---|---|---|---|---|---|
| Ferreri 2001[28] | 0.245 | 0.239 | 0.057 | −0.223 | 0.713 | 1.025 | .305 |
| Zhu 2003[31] | 1.251 | 0.248 | 0.061 | 0.766 | 1.737 | 5.052 | .000 |
| Shelton 2005[30] | 0.127 | 0.148 | 0.022 | −0.162 | 0.416 | 0.862 | .389 |
| Corya 2006[29] | −0.229 | 0.184 | 0.034 | −0.589 | 0.132 | −1.244 | .213 |
| Souery 2011[27] | −0.948 | 0.289 | 0.083 | −1.513 | −0.382 | −3.285 | .001 |
| Romera 2012[32] | 0.143 | 0.084 | 0.007 | −0.022 | 0.308 | 1.694 | .090 |
| Bose 2012[33] | −0.196 | 0.092 | 0.009 | −0.377 | −0.015 | −2.121 | .034 |
| Petrescu 2014[34] | −0.200 | 0.260 | 0.067 | −0.709 | 0.308 | −0.772 | .440 |
| Combined estimate | 0.031 | 0.147 | 0.022 | −0.258 | 0.319 | 0.207 | .836 |




Bschor, J Clin Psychiatry 2016

# The SUN☺D Trial

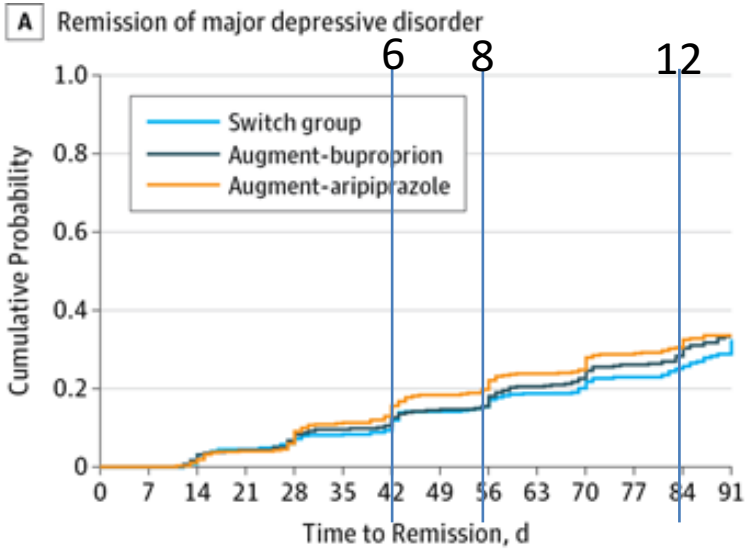
- Open-label randomized (N=2011)
- Step 1 – sertraline 50 mg vs. 100 mg x 3 weeks
  - -> No difference in outcomes or S/E
- Step 2 - non-resp RND to 1) sertraline vs. 2) add mirtazapine vs. 3) switch to mirtazapine x 6 more wks
  - -> Small benefit to both add MRT or switch to MRT vs. continuing sertraline (NNT = 11 for combo, 12 for switch)
  - -> More drop-outs, but not more side effects in combo and switch
  - -> No difference between the combo or switch groups

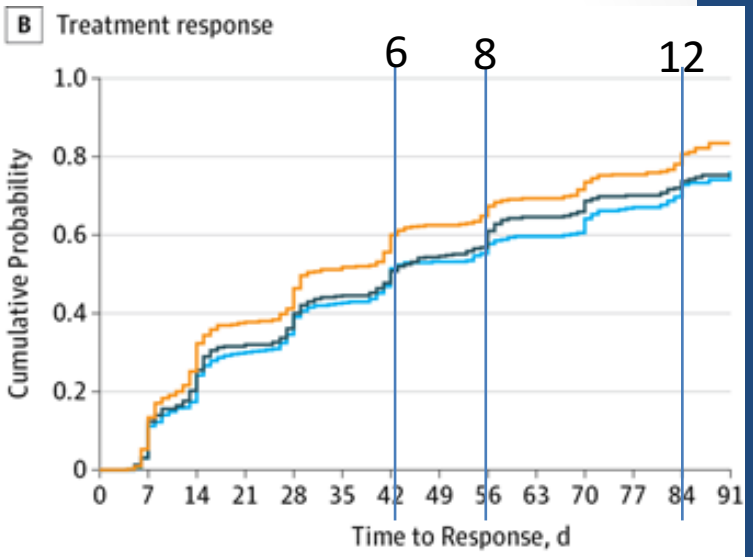
Kato, *BMC Medicine*, 2018. 103

# The VAST-D Trial

- N=1522, 85% male, 12 wk RCT
- SSRI/SNRI/mirtazapine resistant MDD
- Switch to bupropion vs add bupropion vs add aripiprazole
- Small benefit for adding aripiprazole
  - NNT = 8 vs. switch; 12 vs. add bupropion
- Aripiprazole group had:
  - less anxiety
  - more sedation
  - 25% gained >7% wt at 36 weeks.

Mohamed, JAMA, 2017




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Switch group | 511 | 477 | 428 | 379 | 331 | 292 | 221 |
| Augment-buproprion | 506 | 475 | 431 | 387 | 352 | 305 | 247 |
| Augment-aripiprazole | 505 | 467 | 427 | 383 | 341 | 307 | 245 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 511 | 395 | 294 | 218 | 173 | 141 | 77 |
| 506 | 386 | 292 | 223 | 174 | 124 | 79 |
| 505 | 357 | 272 | 198 | 149 | 116 | 72 |

Table 3. Treatment Comparisons for Remission and Response at Week 12 Among Patients With Antidepressant-Resistant Major Depressive Disorder, Acute Treatment Phase[a]

| | Difference (95% CI), %[b] | Relative Risk (95% CI) | *P* Value |
|---|---|---|---|
| **Remission (Primary Outcome)[c]** | | | |
| Augment-bupropion vs switch group | 4.6 (−0.1 to 9.9) | 1.20 (0.97 to 1.50) | .09 |
| Augment-aripiprazole vs switch group | 6.6 (1.3 to 12.0) | 1.30 (1.05 to 1.60) | .02[d] |
| Augment-aripiprazole vs augment-bupropion | 2.0 (−3.5 to 7.6) | 1.08 (0.88 to 1.31) | .47 |
| **Response (Secondary Outcome)[e]** | | | |
| 50% Reduction in QIDS-$C_{16}$ score | | | |
| Augment-bupropion vs switch group | 3.2 (−2.7 to 9.1) | 1.05 (0.96 to 1.15) | .29 |
| Augment-aripiprazole vs switch group | 11.8 (6.2 to 17.5) | 1.19 (1.09 to 1.29) | <.001 |
| Augment-aripiprazole vs augment-bupropion | 8.6 (3.0 to 14.3) | 1.13 (1.04 to 1.23) | .003 |
| Improvement in CGI Improvement score | | | |
| Augment-bupropion vs switch group | 4.6 (−0.9 to 10.2) | 1.07 (0.99 to 1.15) | .10 |
| Augment-aripiprazole vs switch group | 9.5 (4.2 to 14.9) | 1.14 (1.06 to 1.22) | <.001 |
| Augment-aripiprazole vs augment-bupropion | 4.9 (−0.3 to 10.1) | 1.07 (1.00 to 1.14) | .07 |

Abbreviations: CGI, Clinical Global Impression; QIDS-$C_{16}$, 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated.

[a] Treatment comparisons were determined by relative risk ratio from log-binomial regression models stratified by site. The 3 treatment groups: switch to another antidepressant, bupropion sustained release (switch group); augment current treatment with bupropion sustained release (augment-bupropion group); or augment current treatment with an antipsychotic, aripiprazole (augment-aripiprazole group).

[b] Absolute difference in percentage of patients with events between treatments.

[c] Remission was defined as a QIDS-$C_{16}$ score (range, 0-27; 0 indicates better symptoms, 27 indicates worse symptoms) of 5 or less for 2 consecutive weeks after baseline during the acute treatment phase.

[d] *P* value less than .025 for second familywise test of co-primary hypothesis.

[e] Response was defined as reduction in QIDS-$C_{16}$ score of 50% or more from baseline at any scheduled visit after baseline through week 12 or improvement in CGI Improvement score (range, 1-7) of 2 (much improved) or 1 (very much improved) at any scheduled visit after baseline through week 12.

**Table 11.** Recommendations for Adjunctive Medications for Nonresponse or Partial Response to an Antidepressant.

| Recommendation | Adjunctive Agent | Level of Evidence | Dosing |
|---|---|---|---|
| First line | Aripiprazole | Level 1 | 2-15 mg |
| | Quetiapine | Level 1 | 150-300 mg |
| | Risperidone | Level 1 | 1-3 mg |
| Second line | Brexpiprazole[a] | Level 1 | 1-3 mg |
| | Bupropion | Level 2 | 150-300 mg |
| | Lithium | Level 2 | 600-1200 mg (therapeutic serum levels) |
| | Mirtazapine/mianserin | Level 2 | 30-60 mg |
| | Modafinil | Level 2 | 100-400 mg |
| | Olanzapine | Level 1 | 2.5-10 mg |
| | Triiodothyronine | Level 2 | 25-50 mcg |
| Third line | Other antidepressants | Level 3 | Various |
| | Other stimulants (methylphenidate, lisdexamfetamine, etc.) | Level 3 | Various |
| | TCAs (e.g., desipramine) | Level 2 | Various |
| | Ziprasidone | Level 3 | 20-80 mg bid |
| Experimental | Ketamine | Level 1 | 0.5 mg/kg, single intravenous dose[b] |
| Not recommended | Pindolol | Level 1 (lack of efficacy) | Not applicable |

TCA, tricyclic antidepressant.
[a]Newly approved since the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.
[b]For acute treatment.

CANMAT 2016

# Psychotherapies

- Psychotherapies also effective at this stage
  - CBT most effective and psychodynamic least
  - Supported by Cochrane meta-analysis
  - Most psychotherapy studies use 1 ADM failure
  - Many patients with depression refuse therapy (>70% in STAR*D)

Ijaz., Cochrane Database Syst Rev 2018; 5:CD010558.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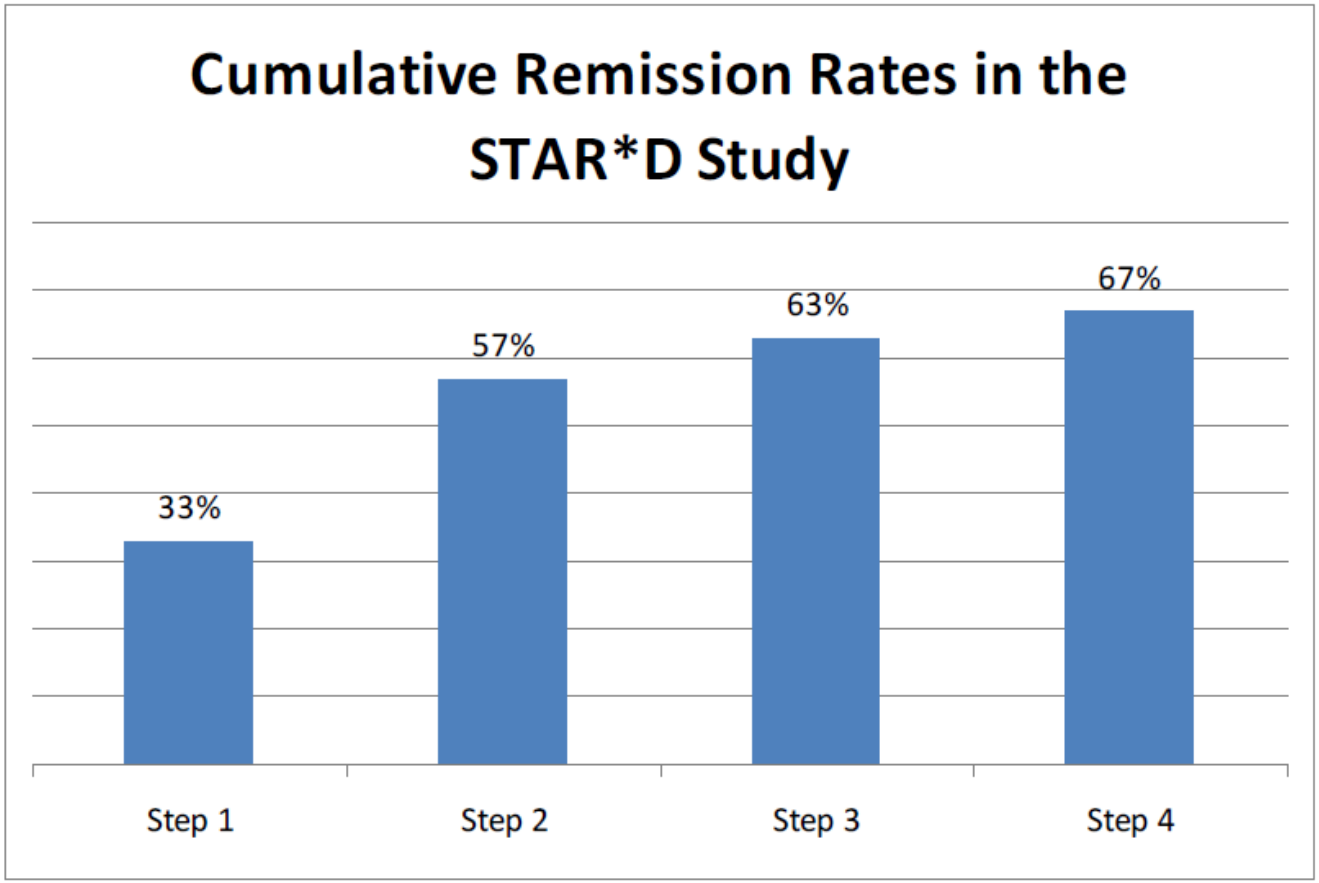
# Treatment resistant depression (TRD)

- 67% do not remit after 1st ADM
- 43% do not remit after 2 ADM
- Diminishing returns after 2 treatments




Israel, J. Pharmaceuticals 2010, 3, 2426-2440

# Treatment Resistant Depression

- No uniform definition exists
- One proposed definition is the failure to remit after an adequate trial of 2 treatments with different mechanisms
  - Includes a depression focused therapy (CBT or IPT >8 weeks)
- Suggests and inflection point at which further treatments may have lower chance of benefit

Conway, et al. *JAMA Psychiatry.* 2017;74(1):9-10.

# Poll

- When I see a patient with treatment resistant depression, I will:

  - A) Usually refer them for follow-up in a psychiatric clinic
  - B) Usually refer them for a psychiatric consultation then resume follow-up with recommendations
  - C) Refer only complex patients with comorbidities for a psychiatric consultation / follow-up
  - D) Usually feel comfortable treating most of them on my own without a psychiatric consultation
  - E) Only refer the most complex or treatment refractory patients for psychiatric assessment

# Approach to Care

- Reassess diagnosis
  - BAD, MDD w/ psychotic features
- Assess for comorbidity
  - SUD, BPD, ADHD, ASD, OCD
- Assess medication adherence, adequacy of trials
- Consider referral

# What works in TRD?

- 2015 network meta-analysis 48 trials, N=6654
  - Quetiapine XR, Aripiprazole, Lithium, Thyroid hormone all effective for TRD
  - SGAs had more robust effect than lithium or thyroid hormone

- 2015 meta-analysis 11 trials N=3341
  - SGAs may be more effective in patients who have failed to benefit from more standard antidepressant trials

Wang, Int J Neuropsychopharm. 2015;18(8) 1-10
Zhou, *J Clin Psychiatry*. 2015; 76(4)e487-498

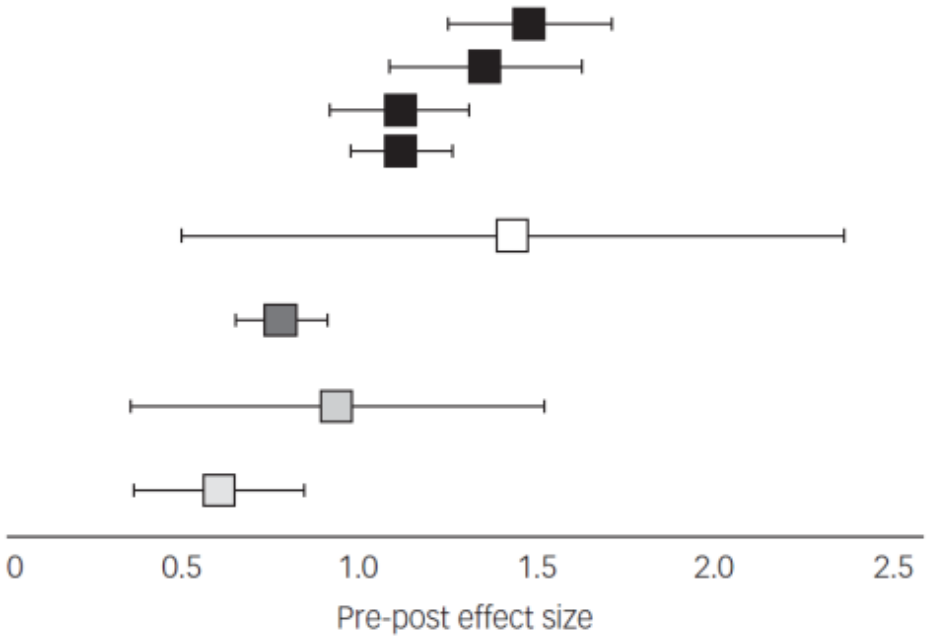
BJPsych | The British Journal of Psychiatry (2019)
214, 42–51. doi: 10.1192/bjp.2018.233

Review

# Augmentation therapies for treatment-resistant depression: systematic review and meta-analysis†

Rebecca Strawbridge, Ben Carter, Lindsey Marwood, Borwin Bandelow, Dimosthenis Tsapekos, Viktoriya L. Nikolova, Rachael Taylor, Tim Mantingh, Valeria de Angel, Fiona Patrick, Anthony J. Cleare and Allan H. Young

| | Treatment class | k | ES |
|---|---|---|---|
| | NMDA-targeting agents | 3 | 1.48 |
| | Pharmacological (other*) | 4 | 1.36 |
| | Mood stabilisers | 8 | 1.12 |
| | Antipsychotics | 10 | 1.12 |
| ** | Psychological therapies | 3 | 1.43 |
| | Pill placebo | 16 | 0.78 |
| | Psychological placebo | 3 | 0.94 |
| | Short-term treatments | 2 | 0.61 |




** used different definition of TRD

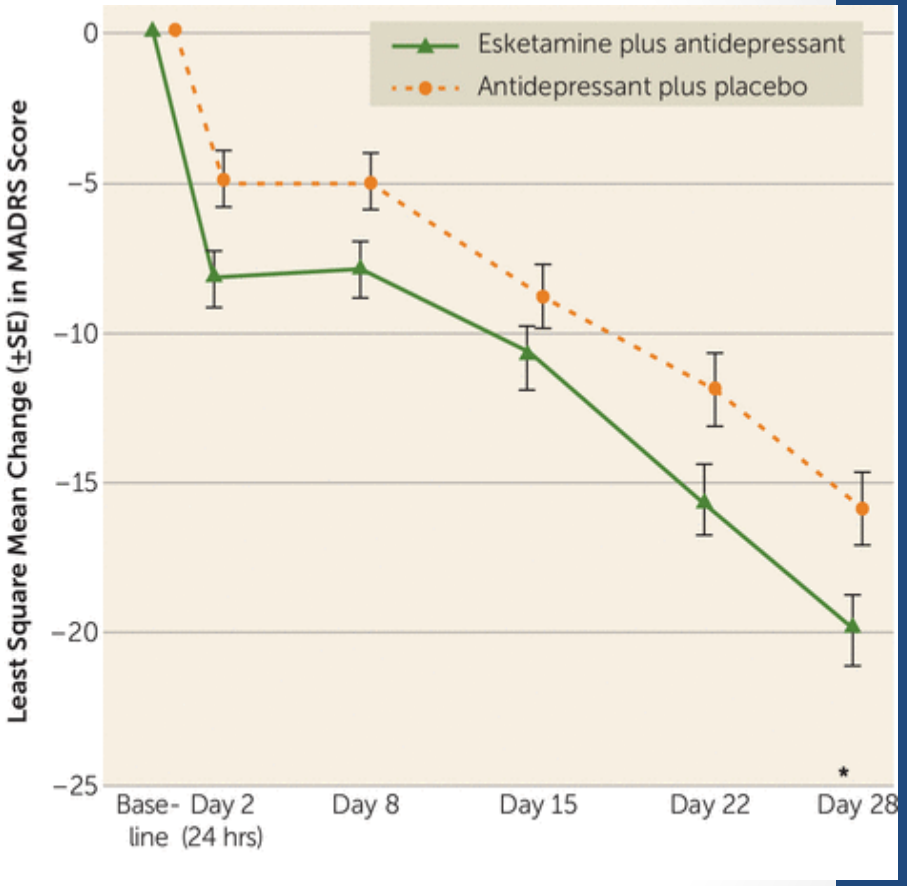
**Table 1** Details of all studies included in this review

| Reference | Intervention | Continent of trial | TRD definition used (number of unsuccessful treatments) | Setting | Comorbidity | Continuation treatment(s) | Continuation therapy |
|---|---|---|---|---|---|---|---|
| Mood stabilisers | | | | | | | |
| Nierenberg *et al*[20] | Lithium/placebo | North America | 1+ adequate ADM (retrospective), plus 6 weeks prospective ADM | OP | Some | NOR | Mono |
| Girlanda *et al*[15] | Lithium/TAU | Europe | 2+ adequate ADM | OP | Frequent psychiatric | TAU | Mono/Poly |
| Schindler *et al*[38] | Lithium/lamotrigine | Europe | 2+ ADM >6 weeks | IP | Some | NR | Mono |
| Barbee *et al*[27] | Lamotrigine/placebo | North America | 1+ ADM >6 weeks (retrospective), plus 8 weeks prospective ADM | NR | None prominent | PAR | Mono |
| Santos *et al*[21] | Lamotrigine/placebo | South America | 2+ adequate ADM | OP | Some | Any ADM | Mono |
| Antipsychotics | | | | | | | |
| Berman *et al*[29] | Aripiprazole/placebo | North America | 1+ ADM >6 weeks (retrospective), plus 8 weeks prospective ADM | OP | None prominent | ESC, FLU, PAR, SER, VEN | Mono |
| Berman *et al*[30] | Aripiprazole/placebo | North America | 1+ ADM >6 weeks (retrospective), plus 8 weeks prospective ADM | OP | None prominent | ESC, FLU, PAR, SER, VEN | Mono |
| Marcus *et al*[32] | Aripiprazole/placebo | North America | 1+ ADM >6 weeks (retrospective), plus 8 weeks prospective ADM | OP | NR | ESC, FLU, PAR, VEN | Mono |
| Ozaki *et al*[34] | Aripiprazole/placebo | Asia | 1+ ADM >6 weeks (retrospective), plus 8 weeks prospective ADM[a] | OP and IP | None prominent | PAR, FLUV, SER, MIL, DUL | Mono |
| Thase *et al*[22] | Brexpiprazole/placebo | North America/ Europe | 1+ ADM (retrospective), plus 1 prospective ADM | OP | None prominent | ESC, FLU, PAR, SER, DUL, VEN | Mono |
| Thase *et al*[23] | Brexpiprazole/placebo | North America/ Europe | 1+ ADM (retrospective), plus 1 prospective ADM | OP | None prominent | ESC, FLU, PAR, SER, DUL, VEN | Mono |
| Shelton *et al*[35] | Olanzapine/placebo | North America | 2+ ADM >4 weeks (retrospective), plus 6 weeks prospective ADM | OP | None prominent | FLU | Mono |
| Dunner *et al*[26] | Ziprasidone | North America | 1+ ADM >4 weeks (retrospective), plus 6 weeks prospective ADM | OP | None prominent | SER | Mono |
| Psychological therapies | | | | | | | |
| Eisendrath *et al*[18] | MBCT/HEP | North America | 2+ ADM >4 weeks | OP | Some | TAU (ADM) | Poly |
| Fonagy *et al*[12] | LTPP/TAU | Europe | 2+ treatments (≥1 ADM, ≥1 psychological) | OP | Some | TAU | Mono/Poly |
| Hauksson *et al*[25] | CBT/TAU | Europe | 2+ adequate ADM | IP | Frequent psychiatric | Multimodal rehabilitation | Mono/Poly |
| NMDA targets | | | | | | | |
| Heresco-Levy *et al*[16] | D-cycloserine/placebo | Asia | 2+ adequate ADM | OP | None prominent | TAU (ADM) | Mono/Poly |
| Husain *et al*[17] | Minocycline/placebo | Asia | 2+ adequate ADM | OP | None prominent | TAU | Mono/Poly |
| Su *et al*[11] | Ketamine/placebo | Asia | 2+ adequate ADM | OP | Frequent psychiatric | NR | NR |
| Other pharmacological | | | | | | | |
| Moller *et al*[33] | Dexmecamylamine/placebo | All except Oceania | 1+ ADM >6 weeks (retrospective), plus 8 weeks ADM prospective | OP | None prominent | ESC, CIT, FLU, PAR, SER, DUL, VEN | Mono |
| Multiple treatment classes | | | | | | | |
| Bauer *et al*[28] | Quetiapine/lithium | Europe | 2+ ADM (retrospective)[a] | OP and IP | None prominent | Any ADM | Mono |
| Fang *et al*[19] | Risperidone/sodium valproate/buspirone/ trazodone/thyroid hormone | Asia | 2+ adequate ADM (stage 2, Thase and Rush criteria) | OP and IP | Some | PAR | Mono |
| Nierenberg *et al*[36] | Lithium/thyroid hormone | North America | 2+ ADM (from stages 1 to 3 STAR*D study) | OP | Frequent psychiatric | BUP, SER, VEN, CIT | Mono |
| Short-term treatments | | | | | | | |
| Baumann *et al*[24] | Lithium/placebo | Europe | 1+ ADM (retrospective), plus 4 weeks prospective ADM | IP | Some | CIT | Mono |
| McAllister-Williams *et al*[14] | Metyrapone/placebo | Europe | 2+ ADM >6 weeks (Massachusetts General Hospital staging criteria) | OP | None prominent | TAU; serotonergic ADM | Mono/Poly |
| Yoshimura *et al*[13] | Aripiprazole | Asia | 2+ ADM 4 weeks (prospective) | NR | None prominent | PAR, SER | Mono |
| Patkar *et al*[37] | Methylphenidate/placebo | North America, Asia | 2+ ADM >6 weeks[a] | OP | None prominent | Most ADM | Mono |
| Maes *et al*[31] | Pindolol/fluoxetine/placebo | North America | 2+ ADM >4 weeks (stages 2–5, Thase and Rush criteria)[a] | IP | Some (physical) | Trazodone | Mono |

- *"Our findings also confirms previous work indicating that aripiprazole and – to a lesser extent – lithium are effective treatments, supporting their current recommendation as first-line therapies. Although the measured ESs with these two pharmacotherapies are similar to other options, the fact that they have been more thoroughly investigated in a larger number of studies underlines their status as first-choice options"*

# Esketamine

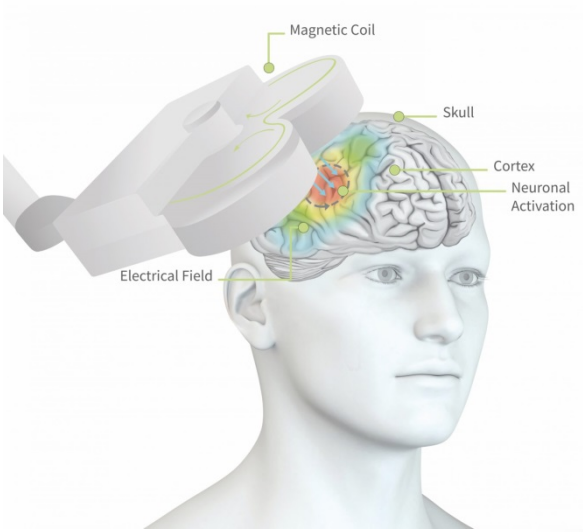
- 2-5 prev AD
- Randomized to:
  - new AD + ESK
  - new AD + placebo
- response
  - 50-60% vs 36-50%
  - NNT 8
- Remission
  - 30-40% vs. 20-24%
  - NNT 6




Popova, Am J Psychiatry. Volume 176. (6) June 2019. 428-43
Citrome. *J Affect Dis.*271, 15 June 2020, 228-23

# rTMS

- Typically involves 5x per week, 45 min sessions
- 2014 meta-analysis for TRD
  - 3x greater response and 5x greater remission than sham control in TRD patients with NNT of 9
  - S/E – well tolerated, occ headaches




https://brainclinics.com/rtms/

*Gaynes, J Clin Psychiatry 2014;75(5):477–489*

# ECT

- May be treatment of choice
  - Psychotic depression
  - Severe suicidality
  - Malnutrition secondary to food refusal
  - Catatonia
  - Recurrent depression with previous good response to ECT

- Older age is associated with a good response. BPD to be associated with decreased ECT efficacy.

# Choosing treatments

- Aripiprazole
  - (+) best studied, ease of dosing, motivation
  - (-) nausea, akathisia, weight gain
- Quetiapine XR
  - (+) anxiety, sleep, mood
  - (-) sedation, ++weight gain
- Lithium
  - (+) anti-suicide, anxiety
  - (-) tremor, sedation, toxicity, need for monitoring

- Thyroid hormone (T3 or L-thyroxine)
  - (+) energy,
  - (-) anxiety, tachycardia
- rTMS
  - (+) well tolerated
  - (-) availability, cost, 5x per week
- Esketamine
  - (+) rapid response, anti-suicide
  - (-) cost, office administration, transient HTN

# Poll

- Regarding each of the following treatments, rate your experience/comfort with…

Aripiprazole (2-5 mg) or quetiapine XR (150-300 mg)

- A) I am very comfortable using them / use them frequently
- B) I have used them occasionally
- C) I have treated several patients who have taken them, but don't start them myself
- D) I have rarely/never used them or seen patients who have taken them
- E) I did not realize they were used for TRD

# Poll

- Regarding each of the following treatments, rate your experience/comfort with…

Lithium (for unipolar depression augmentation)

- A) I am very comfortable using it / use it frequently
- B) I have used it occasionally
- C) I have treated several patients who have taken it, but don't start it myself
- D) I have rarely/never used it or seen patients who have taken it
- E) I did not realize it was used for TRD

# Poll

- Regarding each of the following treatments, rate your experience/comfort with…

rTMS

  - A) I refer patients for it frequently
  - B) I have referred patients for it occasionally
  - C) I have treated several patients who have used it
  - D) I have rarely/never seen patients who have used it
  - E) I did not realize it was used for TRD

# Poll

- Regarding each of the following treatments, rate your experience/comfort with…

Esketamine / ketamine

- A) I refer patients for it frequently
- B) I have referred patients for it occasionally
- C) I have treated several patients who have used it
- D) I have rarely/never seen patients who have used it
- E) I did not realize it was used for TRD

# Refractory depression

- TCAs – Comorbid pain. No clear superiority over SSRIs/SNRIs
- MAOIs – Used by experts due to drug Ix and diet restrictions
- Botulinum toxin
- celecoxib
- Minocyline, D-cycloserine
- Stimulants, modafinil
- Pramipexole
- Surgical approaches

Thase, Connolly, UpToDate, 2020

# Pramipexole

- D2 agonist used for RLS and Parkinson's
- 2013 RCT N=60
  - benefit in unipolar depression
  - trend toward being more beneficial in 2+ ADM failures
- 2016 case series N=46 MDD or Bipolar Depression
  - Highly resistant Mean 6 failed ADM trials, ½ failed ECT
  - 76% had response or remission
  - Mean dose 2.46 mg

- Most helpful for patients with fatigue and anhedonia
- S/E nausea, sleep problems, compulsive beh

Fawcett, 2016. *Am J Psychiatry* 173:2
Cusin, 2013. *J Clin Psychiatry*, 74(7).e636-41

# Principles of Individualizing Treatment
## a.k.a. The Art of Psychopharmacology

- If the patient has a comorbid condition, pick a drug that can treat both depression and that problem
- Choose a medication that has a lower propensity for side effects that bother the patient
- Consider picking a drug with a different or additional mechanism of action
- Make one change at a time