مدیریت افسردگی مقاوم به درمان

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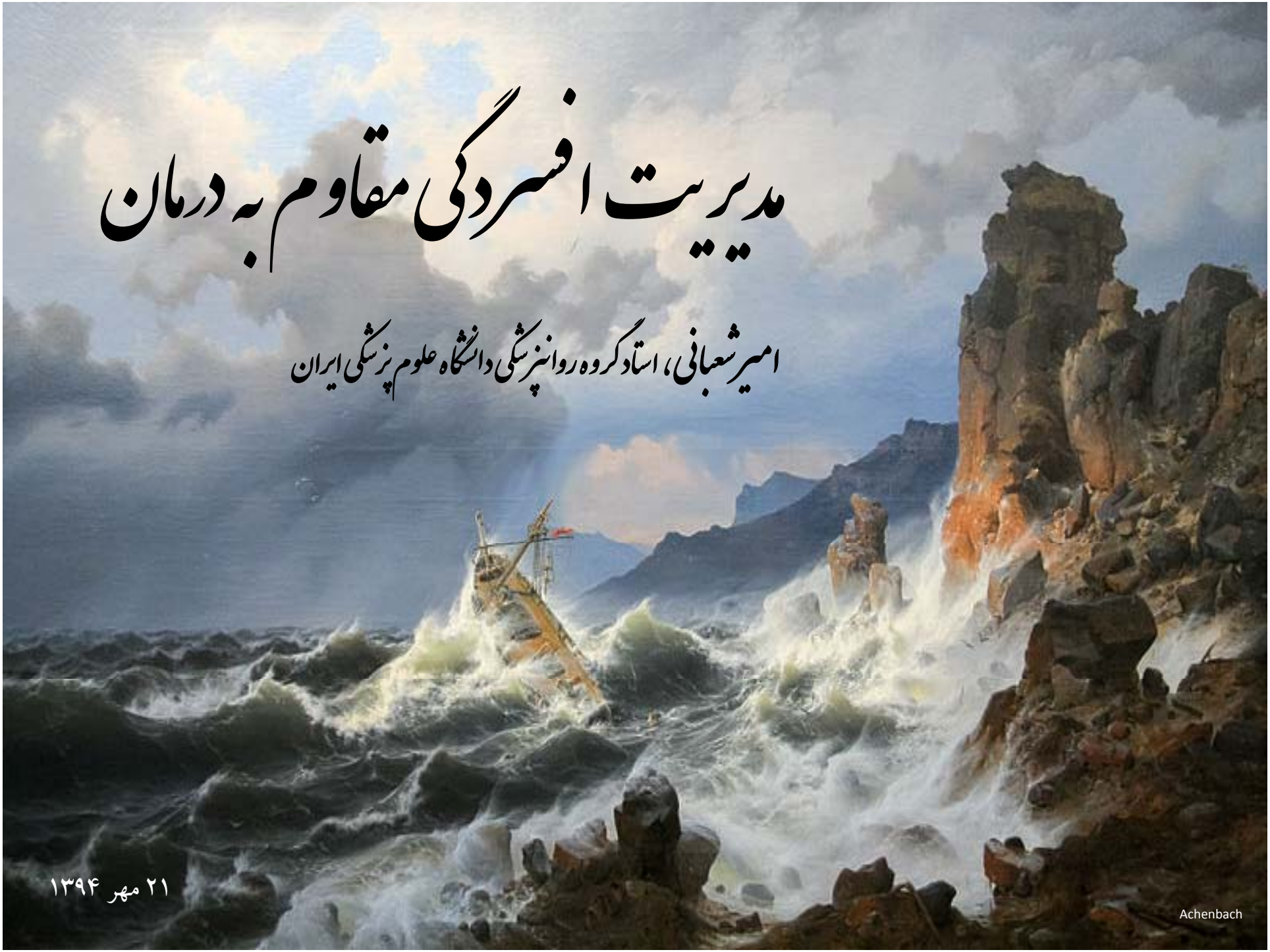


Treatment resistant depression (TRD)

- **TRD is not an untreatable disease.**

Definitions

- **Response:** a 50% reduction in depressive symptom severity
- **Remission:** virtually asymptomatic status (eg, HRSD=7) for at least 2 consecutive weeks
- **Recovery:** Remission for 6 consecutive months

Definitions of TRD

1- Medication failure method

at least 2 treatment trials failure from different classes, each used in an adequate dose for an adequate time period

(McIntyre R.S, etal. Journal of Affective Disorders 2014;156:1–7)

Definitions of TRD

1- Medication failure method

at least 2 treatment trials failure from different classes, each used in an adequate dose for an adequate time period

2- Staging models

Thase and Rush Staging Method (TRSM) (1997)

European Staging Method (ESM) (Souery, et al., 1999)

Massachusetts General Hospital Staging Method (MGH-s) (Petersen, et al., 2005)

Maudsley Staging Method (MSM) (Fekadu , et al., 2009)

(McIntyre R.S, etal. Journal of Affective Disorders 2014;156:1–7)

Thase and Rush staging method: Antidepressant treatment resistance

(1997)

Stage	Description
Stage 0	Any medication trials, to date, determined to be inadequate
Stage I	Failure of ≥1 adequate trial of 1 major class of antidepressants
Stage II	Failure of ≥2 adequate trials of ≥2 distinctly different classes of antidepressants
Stage III	Stage II resistance plus failure of an adequate trial of a tricyclic antidepressant
Stage IV	Stage III resistance plus failure of an adequate trial of an monoamine oxidase inhibitor
Stage V	Stage IV resistance plus a course of bilateral electroconvulsive therapy

(1999)

The European staging method for treatment-resistant depression

Stage	Definition	Duration of trial
A. Nonresponder	Nonresponse to 1 adequate antidepressant trial of: TCA, SSRI, MAOI, SNRI, ECT, or other antidepressant(s)	6 to 8 weeks
B. TRD	Resistance to ≥2 adequate antidepressant trials	TRD 1: 12 to 16 weeks TRD 2: 18 to 24 weeks TRD 3: 24 to 32 weeks TRD 4: 30 to 40 weeks TRD 5: 36 weeks to 1 year
C. CRD	Resistance to several antidepressant trials, including augmentation strategy	≥12 months

CRD: chronic resistant depression; ECT: electroconvulsive therapy; MAOI: monoamine oxidase inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TRD: treatment-resistant depression.

(2005)

Massachusetts General Hospital staging method for treatment-resistant depression

Stage	Description	Points toward resistance score
1	No response to each adequate (≥6 weeks of an adequate dosage of an antidepressant) trial of a marketed antidepressant	1 point per trial (overall score of resistance)
2	Optimization of dose, optimization of duration, and augmentation or combination of each trial (based on the Massachusetts General Hospital or Antidepressant Treatment Response Questionnaire)	0.5 point per trial per optimization/strategy
3	Electroconvulsive therapy	3 points

Source: Reference 57.

Maudsley Staging Method for treatment-resistant depression: Recommended scoring conventions

Parameter/ dimension	Parameter specification	Score
Duration	Acute (≤12 months)	1
	Sub-acute (13 to 24 months)	2
	Chronic (>24 months)	3
Symptom severity (at baseline)	Subsyndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychosis	4
	Severe with psychosis	5
Treatment failures		
Antidepressants	Level 1: 1 to 2 Medications	1
	Level 2: 3 to 4 Medications	2
	Level 3: 5 to 6 Medications	3
	Level 4: 7 to 10 Medications	4
	Level 5: >10 Medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy	Not used	0
	Used	1
Total		15

(2009)

(Fekadu , et al., 2009)

Treatment Pseudoresistance

1. Incorrectly conducted antidepressant treatment (inadequate dosing: the primary reason for treatment failures)
2. Non-compliance (20%)
3. Secondary gain from illness
4. Unrecognized psychosocial factors causing or maintaining depression
5. Unrecognized somatic comorbidity, or misdiagnosis of a somatic disease as depression
6. Unrecognized psychiatric comorbidity, or misdiagnosis of another psychiatric disease as depression
7. Pharmacogenic depression

(Bschor, Bauer, and Adli, 2014)

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study

- **USA**
- **The largest prospective study investigating sequential treatment outcomes**
- **Over 4000 participants with non-psychotic depression**

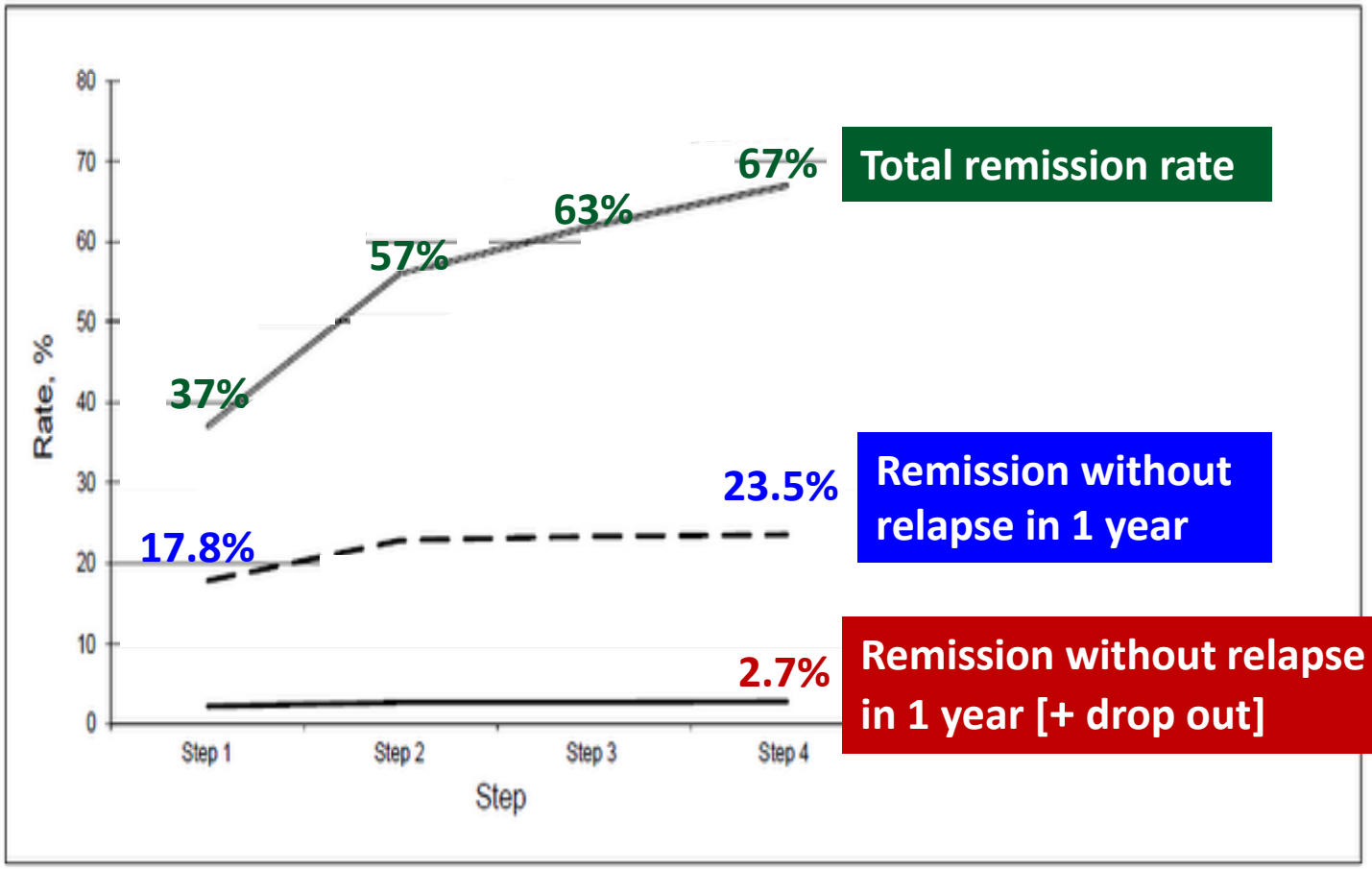
STAR*D algorithm: Treatment levels

Initial 12-week treatment trial

Level 1	**Citalopram** (Celexa)	
Level 2	**Patients could choose one of the following:**	
	SWITCH	AUGMENT
	(stop citalopram, be randomized to receive one of the following)	(keep citalopram, be randomized to also receive one of the following)
	Bupropion sustained-release (Wellbutrin SR) Venlafaxine extended-release (Effexor XR) Sertaline (Zoloft) Cognitive therapy*	Bupropion sustained-release Buspirone (BuSpar) Cognitive therapy*
Level 2a	SWITCH	
(only for those receiving cognitive therapy in level 2)	(stop cognitive therapy, be randomized to receive one of the following) Bupropion sustained-release or Venlafaxine extended-release	
Level 3	**Patients could choose one of the following**	
	SWITCH	AUGMENT
	(stop current therapy, be randomized to receive one of the following)	(keep current therapy, be randomized to also receive one of the following)
	Mirtazapine (Remeron) Nortriptyline (Pamelor)	Lithium T3 thyroid hormone (Cytomel)
Level 4	SWITCH	
	(stop current therapy, be randomized to receive one of the following) Tranylcypromine (Parnate) Mirtazapine plus venlafaxine extended-release	

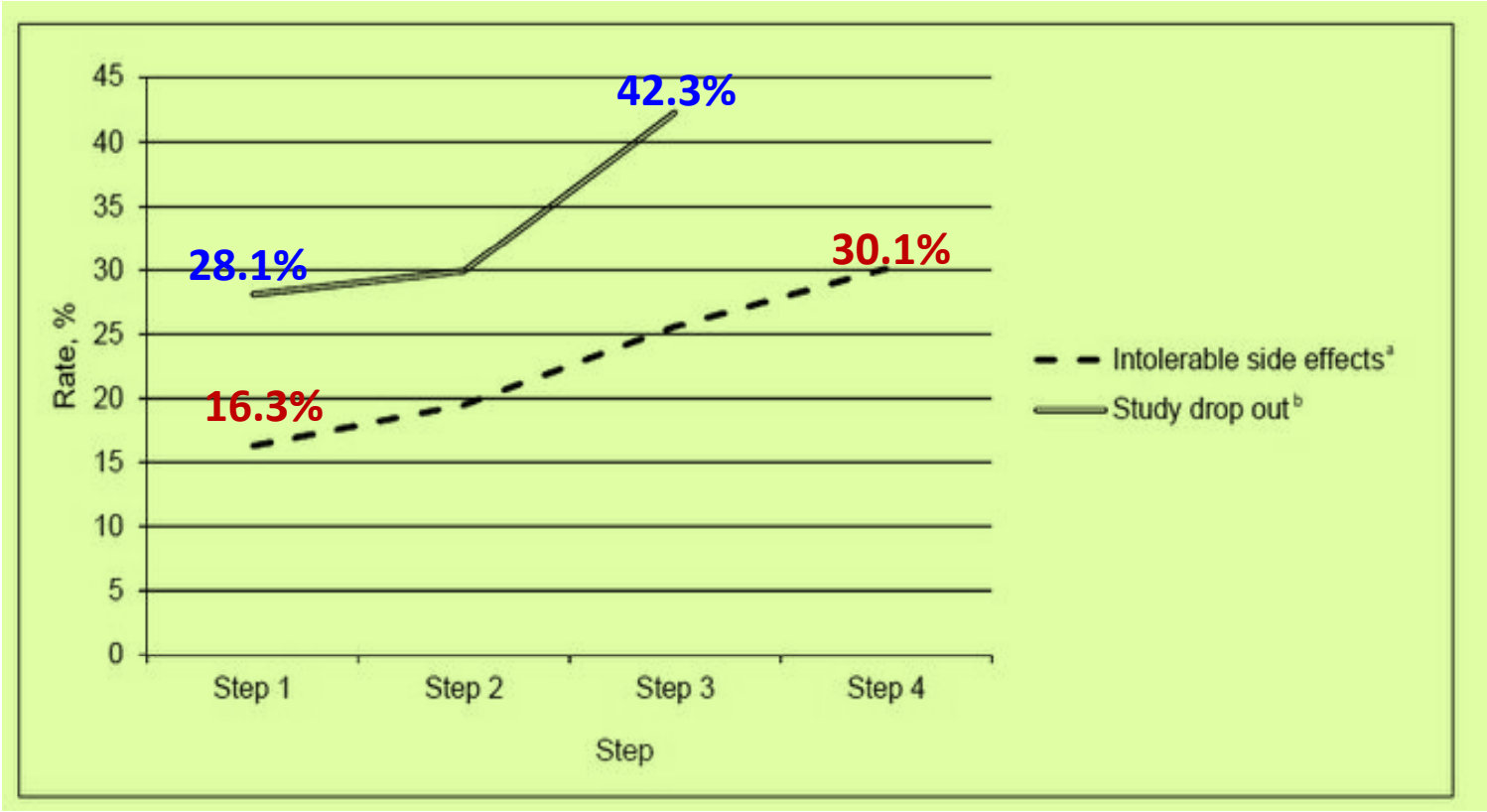
*Patients could refuse cognitive therapy as a randomization option. All treatments were unblinded. Patients advanced to successively higher treatment levels if they failed to achieve remission with their current regimen.

STAR*D



(Pigott HE, 2015)

STAR*D



(Pigott HE, 2015)

Clinical Guidelines

BAP	**2015**	**British Association for Psychopharmacology guidelines**
WFSBP	**2013**	**World Federation of Societies of Biological Psychiatry**
APA	**2010**	**USA; American Psychiatric Association**
CANMAT	**2009**	**Canadian Network for Mood and Anxiety Treatments**
NICE	**2009**	**Britain; National Institute for Health and Clinical Excellence**
CPG	**2004**	**Australian and New Zealand Clinical Practice Guidelines**

Trivedi MH, Rush AJ, Crismon ML, et al. Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project. Arch Gen Psychiatry. 2004;61(7):669–80.
Ricken R, Wiethoff K, Reinhold T, et al. Algorithm-guided treatment of depression reduces treatment costs–results from the randomized controlled German Algorithm Project (GAPII). J Affect Disorders. 2011;134(1–3):249–56.

Antidepressant medication: Minimum effective dosing

Drug class	Antidepressant	Minimum effective dose (mg/d)	
		ATHF	MPG
SSRI	Citalopram	20	20
	Escitalopram	10	10
	Fluoxetine	20	20
	Fluvoxamine	200	50
	Paroxetine	20	20
	Sertraline	100	50
TCA	Amitriptyline	200	75
	Clomipramine	200	75
	Doxepin	200	75
	Imipramine	200	75
	Nortriptyline	76	75
	Trimipramine	200	75
	Desipramine	200	[a]
	Maprotiline	200	[a]
	Protriptyline	41	41

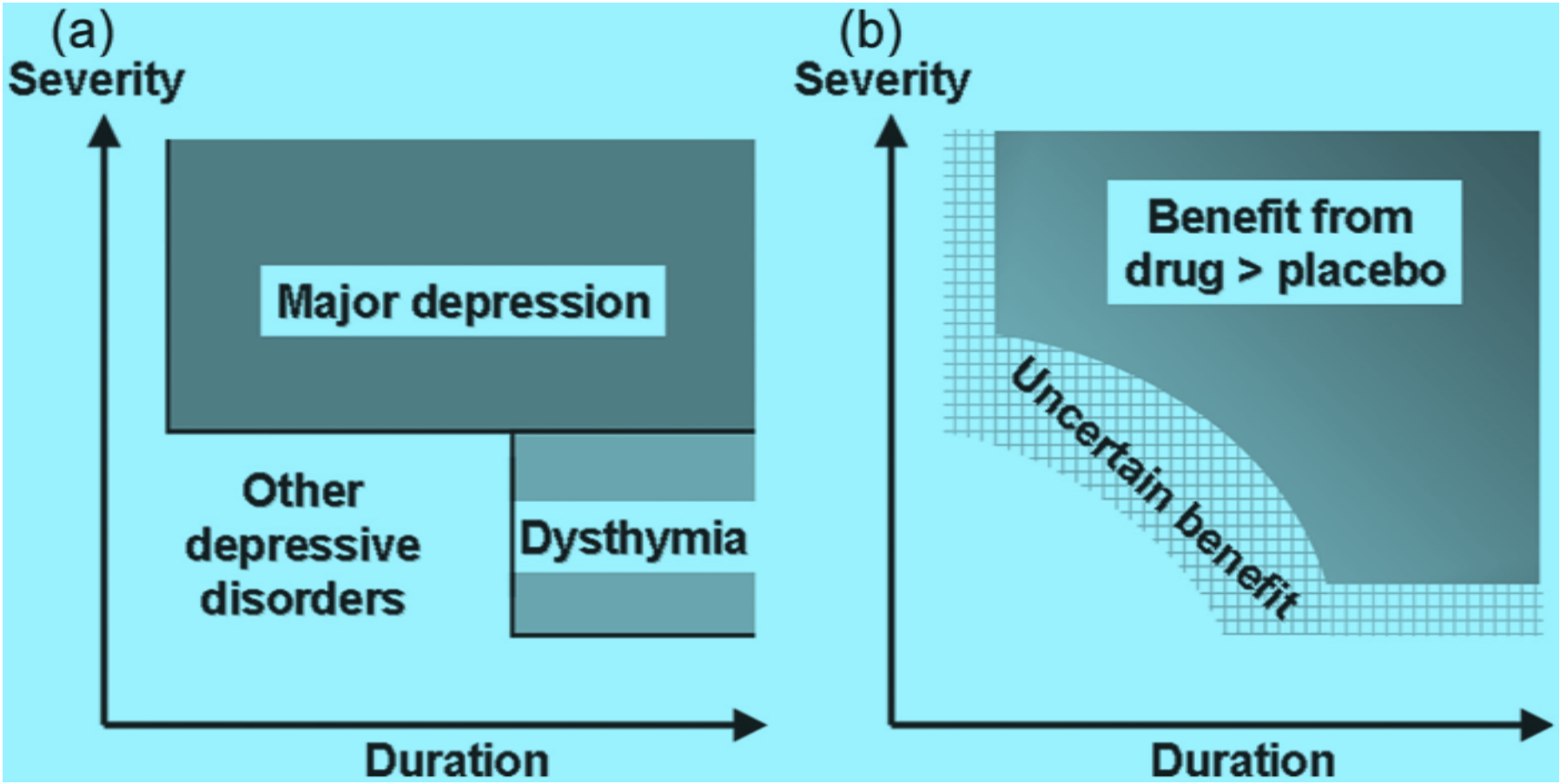
Antidepressant medication: Minimum effective dosing

Drug class	Antidepressant	Minimum effective dose (mg/d)	
		ATHF	MPG
MAOI	Isocarboxazid	41	30
	Phenelzine	61	45
	Tranylcypromine	41	20
	Selegiline	41	41
	Selegiline (TD)	9	[a]
SNRI	Duloxetine	40	60
	Venlafaxine	225	75
TeCA	Mirtazapine	30	30
	Amoxapine	400	[a]
SARI	Nefazodone	300	[a]
	Trazodone	400	150
NRI	Reboxetine	8	8
NDRI	Bupropion	300	[a]

Approach

1. Evidence-based
2. Diagnosis-based
3. Symptom-based
4. Disorder feature-based
5. Patient feature-based
6. Pharmacodynamic-based

Diagnosis-based



A dimensional approach to depressive disorders and response to treatment

(Cleare A, et al. Journal of Psychopharmacology 2015;29(5):459-525)

Symptom-based

- Sleep
- Psychomotor
- Appetite
- Weight
- Suicidality
- Aggression
- Anxiety
- Bipolar-like symptoms
- …

Disorder feature-based

- Recurrence rate
- Psychotic
- Atypical
- Age at onset
- Severity
- …

Patient feature-based

- Age
- Gender
- Fertility
- Family history
- Compliance
- Personality
- Comorbidity
- Genetic factors
- …

Therapeutic options

1	**Optimization**	Maximize dose; adequate time; check serum level
2	**Combination**	Antidepressant + antidepressant
3	**Augmentation**	Antidepressant + non-antidepressant medicine
4	**Switching**	
5	**Somatic therapies**	ECT, VNS, rTMS, MST, DBS, tDCS
6	**Integrated approach**	•Antidepressant + psychotherapy •Risk management strategies •Complementary and alternative medicine •Life style changes such as exercise and school vacation

(Al-Harbi K., et al., 2012)

Antidepressant agents

TCAs (imipramine)	**NDRIs** (bupropion)
Atypical TCAs (mianserin)	**NASSAs** (mirtazapine)
MAOIs (tranylcypromine)	**MASSAs** (agomelatine)
RIMAs (moclobemide)	**SSREs** (tianeptine)
SSRIs (fluoxetine)	**SRI+5HT$_{1a}$PA** (Vilazodone)
SNRIs (venlafaxine)	**SNDRIs** (Amitifadine)
NRIs (reboxetine)	**Herbal**: St. John's wort
SARIs (trazodone)	**Serotonin Modulator and Stimulator** (Vortioxetine)

Atypical antipsychotics

- With the most robust evidence
- In most studies as adjunctive agents to SSRIs and SNRIs

Lithium

- Augmentation with lithium is less expensive and more effective than augmentation with AAP.

  (Edwards SJ, et al. Health Technol Assess 2013;17(54))

- In most studies as an adjunctive agent to TCAs

Psychotherapy

1. **Cognitive behavioral therapy (CBT):**

   with the most compelling evidence; CBT is recommended if psychological treatment is used as monotherapy for recurrent depression (BAP guideline)

2. **Behavioral activation (BA)**

3. **Interpersonal psychotherapy (IPT):**

   is a type of short-term therapy that was developed specifically for the treatment of acutely depressed patients.

4. **Psychodynamic psychotherapy**

5. **Person-centered therapy (PCT)**

6. **Cognitive behavioral analysis system of psychotherapy (CBASP):**

   CBASP is the only psychotherapeutic method developed specifically for the treatment of chronic depression.

(Bschor, Bauer, and Adli, 2014)

Neurostimulation strategies

- Electroconvulsive therapy (ECT)
- Transcranial direct current stimulation (tDCS)
- Repetitive transcranial magnetic stimulation (rTMS)
- Magnetic seizure therapy (MST)
- Vagus nerve stimulation (VNS)
- Deep brain stimulation (DBS)
- Ablative neurosurgery

Other physical strategies

- Sleep deprivation
- Bright light therapy (Dawn simulation)
- Supervised physical exercise

Complementary treatments

- Omega-3 fatty acids
- Hypericum extracts (St John's Wort)
- S-adenosyl-l-methionine (SAMe)

Electroconvulsive therapy (ECT)

- More effective than antidepressants
- Remission rates around 60% in TRD
- High relapse rates after remission
- First line treatment in cases of depression requiring urgent treatment or psychotic features.
- The efficacy of ECT is enhanced with concomitant use of nortriptyline or VLF. (Sackeim HA, et al. Arch Gen Psychiatry. 2009;66(7):729–37.)

(BAP guideline)

Repetitive transcranial magnetic stimulation (rTMS)

- **The FDA limited the indication to only one treatment failure.**
- **May be an effective short-term treatment but less effective than ECT for psychotic depression**

(Blumberger, et al., 2013)
(BAP guideline)

Vagus nerve stimulation (VNS):

- After failing to respond to "≥4 and 8>" antidepressants
- No positive double-blind RCTs
- One of the largest acute efficacy studies failed to demonstrate a difference from placebo. (Rush AJ, et al. Biol Psychiatry. 2005;58(5):347–54.)
- The remission rates are quite low: The MADRS remission rate for VNS + TAU at 12, 24, 48, and 96 weeks were 3%, 5%, 10%, and 14%. (Berry SM, et al. Med Devices. 2013;6:17–35.)

(Blumberger, et al., 2013)

(BAP guideline)

Transcranial direct current stimulation (tDCS):

- A meta-analysis of 10 studies (6 RCTs): active tDCS more effective than sham tDCS
- tDCS may enhance outcomes in patients with mild to moderate non-treatment resistant depression.

(Blumberger, et al., 2013)

(Kalu UG, et al. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychological medicine 2012:1-10)
Loo CK, Alonzo A, Martin D, et al. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry. 2012;200(1):52–9.

Magnetic seizure therapy (MST):

- A potential alternative to ECT
- "It involves applying a train of high frequency magnetic stimuli to produce electrical current indirectly in the brain via electromagnetic induction to induce a seizure."
- "MST has still only been studied in small open studies and a couple of randomized studies."

(Blumberger, et al., 2013)

Deep brain stimulation (DBS):

- No cognitive adverse effects
- Promising results from open-label studies of stimulation of the subgenual cingulate, medial forebrain bundle and ventral anterior capsule or ventral striatum
- Two as yet unpublished multicentre RCTs evaluating the efficacy of subgenual cingulate cortex or ventral striatum/ventral capsule DBS were recently discontinued due to reported inefficacy.
- In all reports, discontinuation of DBS produced a rapid return of severe symptoms and in a few cases led to suicide.

(BAP guideline)

- **Omega-3 fatty acids**
  - ✓ Total EPA+DHA of 1 g/d
  - ✓ EPA should be ≥60% of total EPA + DHA (Morreale M, 2012; Current Psychiatry)
  - ✓ The more severe the depression, the more likely symptoms will respond
- **Hypericum extracts (St John's Wort)**
  - ✓ Effective in the acute treatment of mild and moderate MDD
  - ✓ Not established longer-term efficacy and safety
  - ✓ Non-standardized preparations
  - ✓ Not recommended as a first-line treatment for depression
- **S-adenosyl-l-methionine (SAMe)** (800-1600 mg/day)

Modest Efficacy/ Weak or Preliminary Evidence

- **Stimulants: methylphenidate/modafinil** (BAP, 2015)
- **Tryptophan addition, especially to MAOIs** (Anderson, 2003)
- **Estrogen in perimenopausal women** (Morgan et al., 2005)
- **Testosterone gel replacement in men; with benefits most apparent in those with low testosterone levels** (Zarrouf et al., 2009)
- **Ketamine:**

✓ **The antidepressant effect usually subsides over the following several days**

- **SAMe (800–1600 mg/day): small numbers of patients, and of highly variable quality**

Modest Efficacy/ Weak or Preliminary Evidence

- **Lamotrigine**
- **Metyrapone: steroid synthesis inhibitor**
- **Dehydroepiandrosterone (DHEA): endogenous steroid hormone**
- **Mifepristone: steroidal antiprogestogen and antiglucocorticoid**
- **Hypericum extracts (St John's Wort):**
  - ✓ **Effective in the acute treatment of mild and moderate MDD**
  - ✓ **Not established longer-term efficacy and safety**

Modest Efficacy/ Weak or Preliminary Evidence

- **Sleep deprivation: most relapse after a night's sleep**
- **Bright light therapy (Dawn simulation):**

✓ **Probable short-term benefit in SAD, and as monotherapy, but not added to antidepressants, in non-seasonal depression**

✓ **Often very short-duration trials (mostly 1 week)**

✓ **Lack of long-term data**

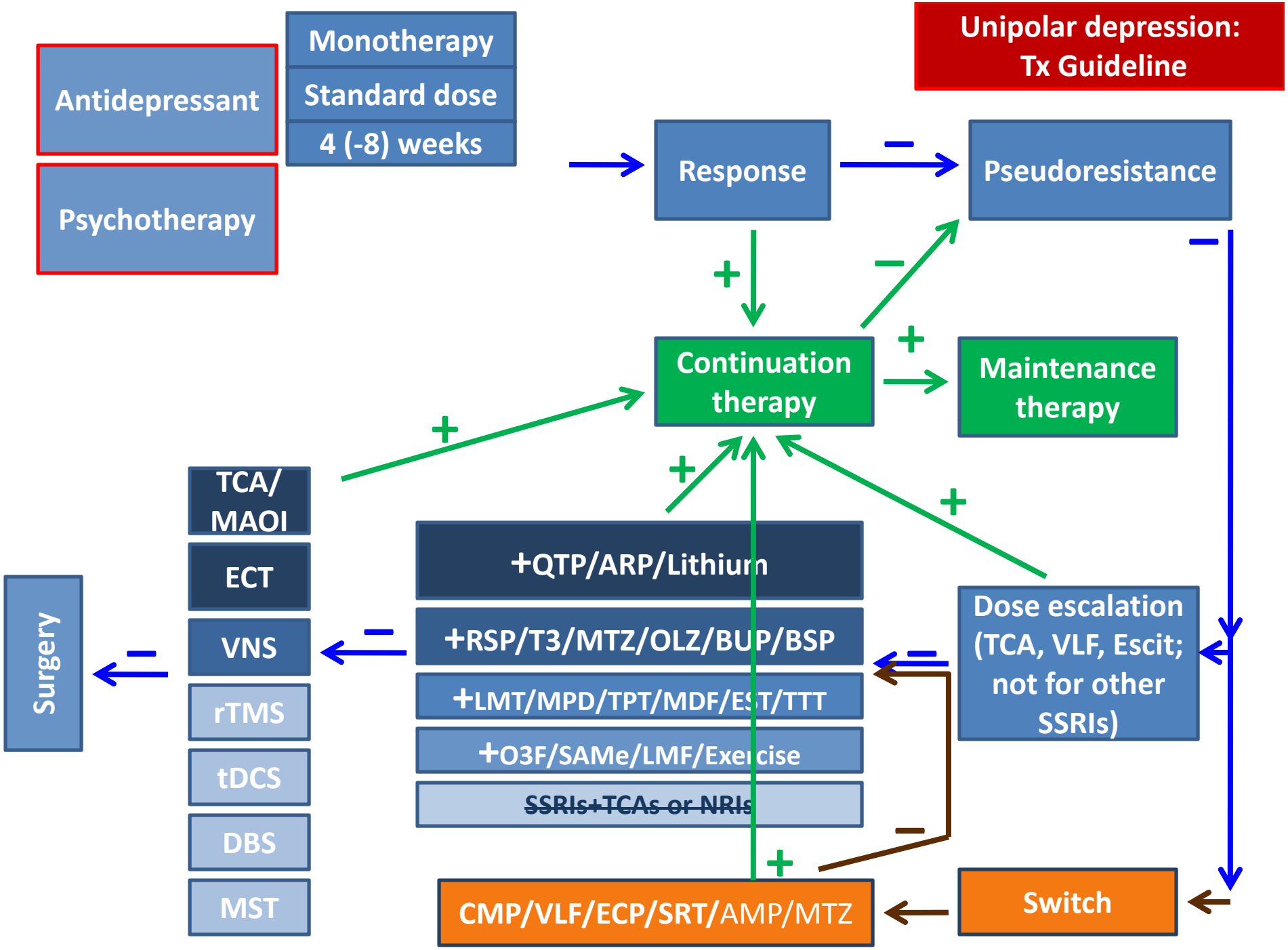
Dawn simulation

Other agents

- **Celecoxib**
- **Infliximab**: TNF antagonist
- **Amantadine**: up to 300 mg/d
- **Carbergoline**: 2 mg/d
- **D-cycloserine**: 1000 mg/d
- **Dexamethasone**: 3-4 mg/d, 4 days
- **Hyoscine**: 4 mcg/kg IV
- **Ketoconazole**: 400–800 mg/d
- **Mecamylamine**: up to 10 mg/d
- **Nemifitide**: 40–240 mg/d, SC
- **Omega-3-TGs**: EPA 1–2 g/d
- **Pramipexole**: 0.125–5 mg/d
- **Riluzole**: 100–200 mg/d
- **Tianeptine**: 25–50 mg/d
- **Zinc**: 25 mg/d
- **Ziprasidone**: up to 160 mg/d

Under question/Ineffective

- +pindolol
- +phenytoin
- +folate
- SSRIs + [TCAs or NRIs]
- Reuptake inhibitors + mianserin
- DBS
- Homeopathy



*(Bschor, Bauer, and Adli, 2014; BAP 2015; STAR*D)*

- **Identifying decision day**