Treatment of Depressive Disorders: Current Evidence Base

Outline

- Basic principles
- Anti-depressants
- Psychotherapy
- Physical exercise
- First, second and third line treatment options
- Treatment of MDD
- Management of treatment refractory depression
- Psychotic depression
- Other treatment options
- Treatment in special populations
- STAR*D trial
- References

Basic Principles

Treatment Phase	Duration	Goals	Activities
Acute and continuation	8-12 weeks	• Achieve symptomatic remission • Monitor side effects • Restore function	• Establish therapeutic alliance • Provide psychoeducation • Select optimal antidepressant treatment(s) • Monitor progress
Maintenance	6-24 months or longer	• Return to full function and quality of life • Prevention of recurrence	• Continue psychoeducation • Rehabilitate • Manage comorbidities • Monitor for recurrence

Basic Principles

- Assessment:
  - Anxiety symptoms
  - substance use
  - suicidality
  - psychotic features
  - bipolarity
  - Psychiatric and medical comorbidities
  - psychosocial, functional factors
  - Concurrent prescription medications

Basic Principles

- Discussion of treatment options with patient: pharmacological and non-pharmacological
- Discussion of likely outcomes
- Regular follow-up, serial assessments including objective assessment and treatment adherence

Anti-depressants

TCA

- First antidepressants
- Block serotonin and nor-epinephrine reuptake
- Adverse effects: anticholinergic side-effects, cardiac arrhythmias (QTc prolongation)
- Toxic in overdose
- Overall tolerability lower than SSRI and SNRI
- Eg: imipramine, amitriptyline, nortriptyline, loxapine, dotheipin.

Anti-depressants

SSRI

SSRI	Dose (mg)	Adverse effects >10% frequency
Citalopram	20–40	Nausea, dry mouth, sweating
Escitalopram	10–20	Male sexual dysfunction and nausea
Fluoxetine	20–60	Nausea, dry mouth, somnolence, nervousness, anxiety, insomnia, tremor, anorexia
Fluvoxamine	100–300	Dry mouth, headaches, somnolence, agitation, insomnia, sweating, tremor, anorexia, dizziness, constipation
Paroxetine	20–60	Nausea, diarrhea, dry mouth, headaches, somnolence, insomnia, sweating, asthenia, male sexual dysfunction, dizziness
Sertraline	50–200	Nausea, diarrhea, dry mouth, headaches,somnolence, insomnia, fatigue, tremor, male sexual dysfunction, dizziness

Anti-depressants

SNRI

SNRI	Dose (mg)	Adverse effects >10% frequency
Venlafaxine	75–375	Headaches, somnolence, dry mouth, dizziness, nervousness, insomnia, sweating, male sexual Dysfunction, nausea
Desvenlafaxine	50–100	Dry mouth, dizziness, nausea, sweating
Duloxetine	30–120	Nausea, dry mouth, constipation, insomnia, male sexual dysfunction
Levomilnacipran	20–80	Nausea, dry mouth, headaches, male sexual dysfunction

Anti-depressants

Other anti-depressants

Other ADs	Dose (mg)	Adverse effects >10% frequency
Agomelatine	25–50	
Bupropion	150–450	Insomnia, dry mouth, nausea, headache
Mirtazapine	15–60	Dry mouth, constipation, increased appetite, weight Gain, somnolence
Trazodone	150-600	Drowsiness, weight gain, orthostatic hypotension, GI distress, cardiac arrythmia
Moclobemide	300–600	
Vilazodone	10–40	Diarrhea, nausea, headaches
Vortioxetine	10–20	Nausea

Psychotherapy

CBT/MCBT

- Cognitive distortions in MDD include selective attention to the negative aspects of circumstances and unrealistically morbid inferences about consequences.
- The goal of cognitive therapy is to alleviate depressive episodes and prevent their recurrence by helping patients identify and test negative cognitions; develop alternative, flexible, and positive ways of thinking; and rehearse new cognitive and behavioral responses

Psychotherapy

CBT/MCBT

- It includes:
  - Identify and challenge automatic thoughts
  - Engage in activities that provide evidence disproving dysfunctional beliefs
  - Modify core beliefs by reviewing evidence
- Effective in MDD
- Variant is mindfulness based CBT

Psychotherapy

BT

- Deficit of reinforcers, including pleasant activities and positive interpersonal contacts
- Increase activity level
- Structured goal setting
- Interpersonal skills training

Psychotherapy

IPT

- Focuses on Interpersonal vulnerabilities arising from early attachment and learned relationship patterns
- It includes:
  - Develop awareness of patterns in primary relationships and the therapeutic relationship
  - Interpersonal skills training
  - Communication analysis

Physical Exercise

- Physical exercise represents an underutilized intervention.
- Can counteract several mechanisms postulated to increase mortality risk in depression.
- Exercise can be as effective as other first-line treatments, while being mostly free of adverse side-effects.
- There is a need of pragmatic trials to evaluate the long-term effects of exercise and its cost-effectiveness.

Physical Exercise

Summary of the aerobic exercise prescription guidelines for healthy and clinical populations and for those with depression.

Author	Frequency (per week)	Intensity	Session duration	Mode of exercise	Intervention duration	Individual or group	Level of supervision
Perraton et al.[23] (depression)	3	60–80%HR_{max}	30 min	Individualized according to preference	8 weeks	Group or individual	Recommended. Qualifications and experience unspecified
NICE[18] (depression)	3	NR	45–60 min	NR	10–14 weeks	Group	Competent practitioner
Garber et al.[24] (healthy population)	≥5	Moderate	Min 30 min/session or ≥150 min/week	Individualized according to preference	Ongoing	NR	Experienced fitness instructor
	≥3	Vigorous	Min 20 min/session or ≥75 min/week Or a combination to achieve ≥500–1000 kcal/week				
Horden et al.[23] (type II diabetes and pre diabetes)	Min 3 with no more than 2 consecutive days without exercise	Moderate (55–69%HR_{max}) or Vigorous (70–89%HR_{max})	Min 210 min/week of moderate or 125 mins/week of vigorous exercise or a combination of both	Walking, running cycling or swimming	Ongoing	NR	Appropriately trained and qualified personnel
Stanton and Reaburn (current review) (depression)	3–4	Low – moderate or patient preferred	30–40 min	Any aerobic activity	9 weeks	Group or individual	Appropriately trained and qualified personnel

NR – not reported.

First Line Treatment

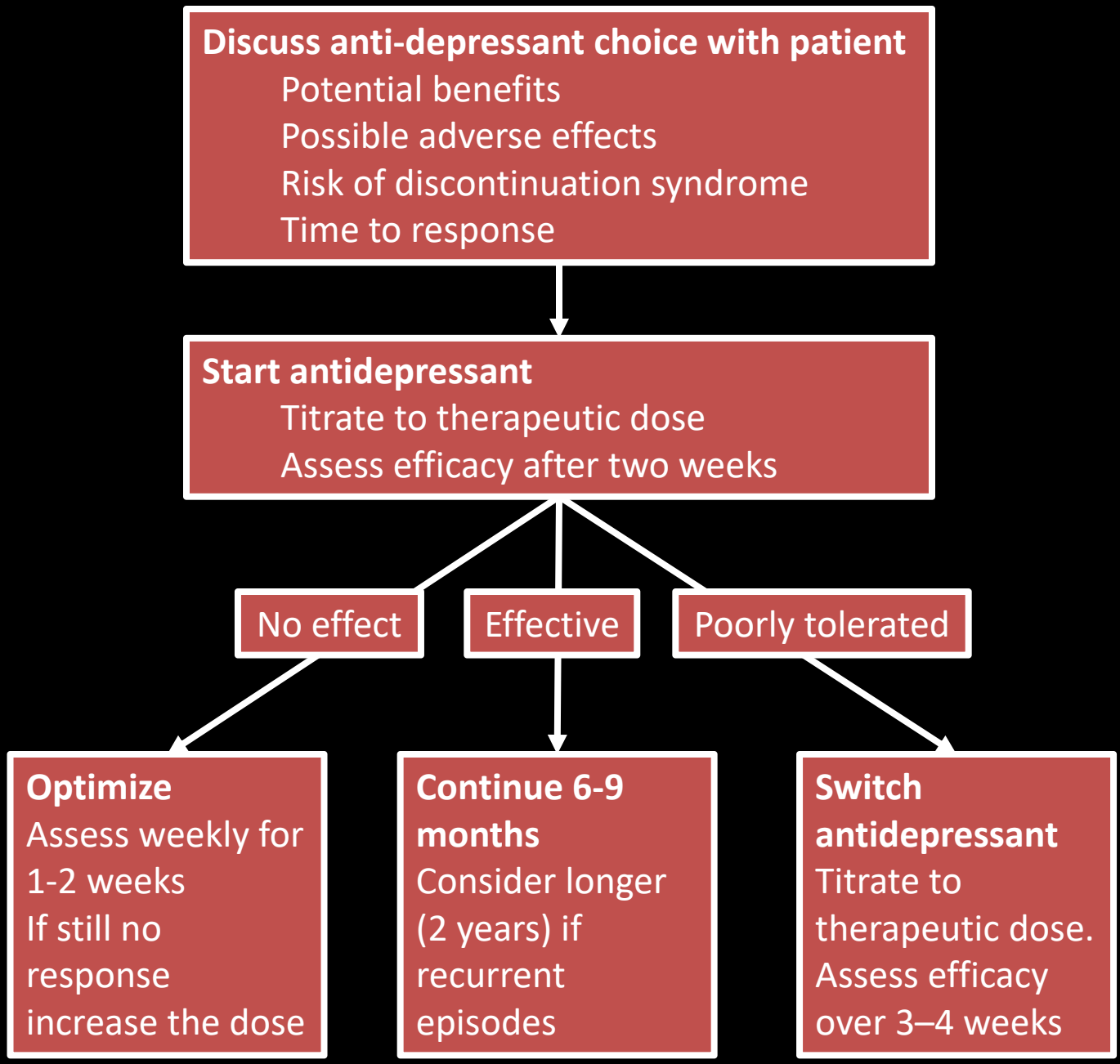
- First line: SSRIs, SNRIs, other second generation, and novel antidepressants.
- **NICE:** SSRI or mirtazapine
  - Mild recent onset depression: CBT/ self-guided help/exercise
- **CANMAT:** SSRIs, SNRIs, agomelatine, bupropion, mirtazapine and vortioxetine
  - Psychoeducation, self-management, and psychological treatments for mild depression
- **APA:** Psychotherapy or second generation anti-depressants or both

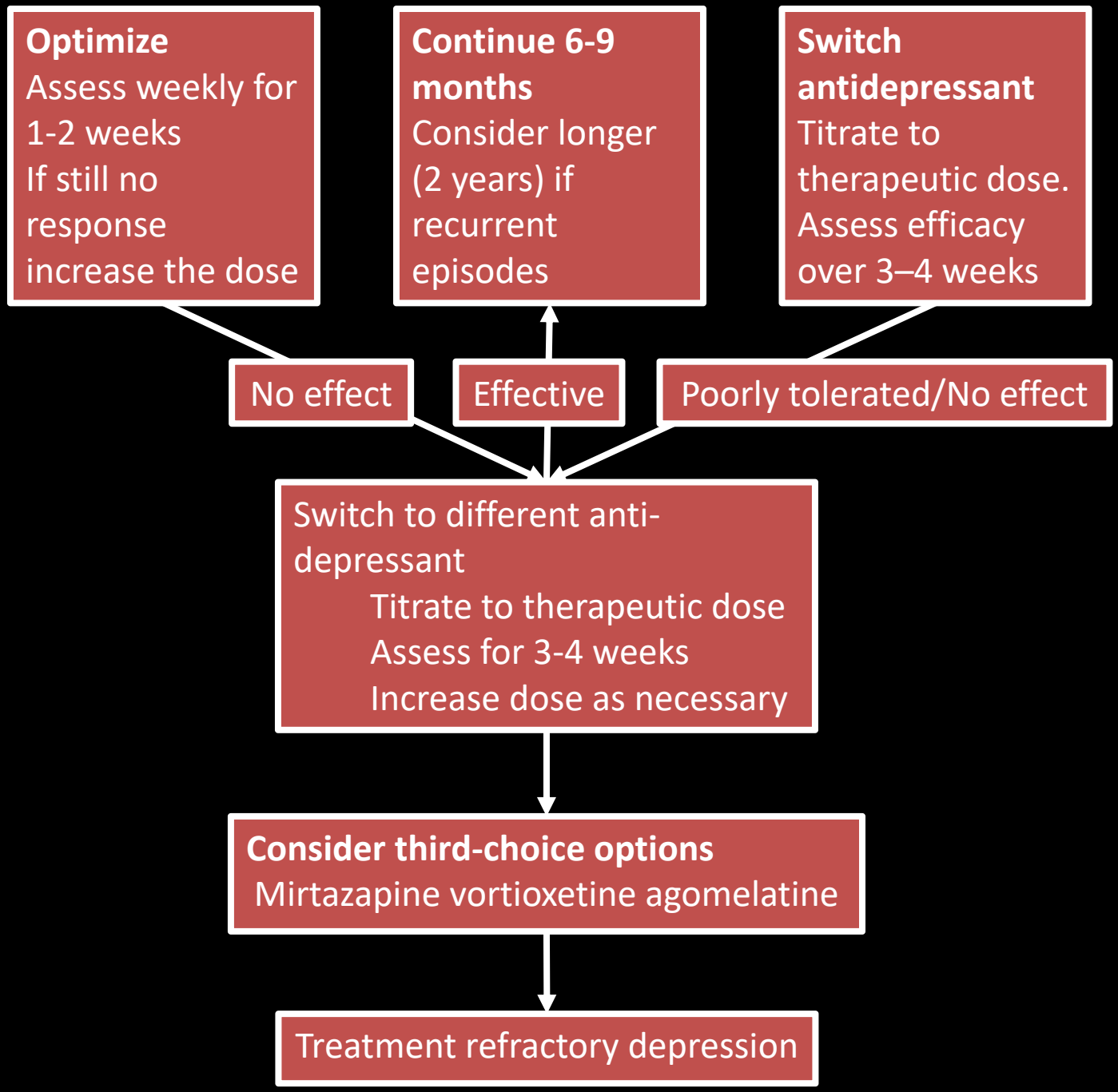
Second Line Treatment

- Optimization/augmentation/ switching
- **NICE:** Augmentation with SGA or adding another anti-depressant
- **CANMAT:** TCAs, quetiapine, trazodone, moclobemide, selegiline, levomilnacipran and vilazodone
- **APA:** Switch to psychotherapy/ another anti-depressant or augment with psychotherapy or pharmacological augmentation strategies

Third Line Treatment

- Third line anti-depressants and adjunctive treatment
- TCA, MAOI
- Augmentation strategies
- Experimental options: ketamine, lamotrigine, tri-iodothyronine
- ECT
- rTMS, vagal nerve stimulation
- Alternative treatment options


Discuss anti-depressant choice with patient
Potential benefits
Possible adverse effects
Risk of discontinuation syndrome
Time to response
Start antidepressant
Titrate to therapeutic dose
Assess efficacy after two weeks
No effect
Effective
Poorly tolerated
Optimize
Assess weekly for 1-2 weeks
If still no response increase the dose
Continue 6-9 months
Consider longer (2 years) if recurrent episodes
Switch antidepressant
Titrate to therapeutic dose.
Assess efficacy over 3–4 weeks


Optimize
Assess weekly for 1-2 weeks
If still no response increase the dose
Continue 6-9 months
Consider longer (2 years) if recurrent episodes
Switch antidepressant
Titrate to therapeutic dose.
Assess efficacy over 3–4 weeks
No effect
Effective
Poorly tolerated/No effect
Switch to different anti-depressant
Titrate to therapeutic dose
Assess for 3-4 weeks
Increase dose as necessary
Consider third-choice options
Mirtazapine vortioxetine agomelatine
Treatment refractory depression

Treatment Refractory Depression (1st Line)

Treatment	Advantages	Disadvantages
Add Lithium	• Well established • Well supported in literature • Recommended by NICE	• Poorly tolerated at higher plasma levels • Potentially toxic • Plasma level monitoring
Olanzapine + Fluoxetine	• Well researched • Usually well tolerated • Olanzapine + TCA may also be effective • Olanzapine alone may be effective	• Weight gain • Most data relate to bipolar depression
Add Quetiapine to SSRI/SNRI	• Good evidence base • Usually well tolerated • Possibly more effective than lithium	• Dry mouth, sedation, constipation • Weight gain
Add Aripiprazole to antidepressant	• Good evidence base • Safe, well tolerated • Low doses may be effective	• Akathisia and restlessness common at standard doses • Insomnia
SSRI + Buproprion	• Supported by STAR*D • Well tolerated	• Not licensed in UK for depression
SSRI + Venlafaxine/ Mianserine/ Mirtazapine	• Recommended by NICE • Well tolerated • Excellent literature support • Widely used	• Serotonin syndrome • Blood dyscrasia (Mianserine) • Wt. gain and sedation (Mirtazapine)

Treatment Refractory Depression (2nd Line)

Treatment	Advantages	Disadvantages
Add Ketamine (intranasal esketamine)	• Rapid Response • High remission rate • Maintained response with repeated doses • Well tolerated at sub-anesthetic doses	• IV needs to be administered in hospital • Cognitive effects • Transient increase in BP, PR, arrhythmias • Repeated dosing • Underestimation of adverse effects
Add Lamotrigine	• Well researched • Widely used • Well tolerated	• Slow titration • Rash • Appropriate dosing unclear
SSRI + Buspirone	• Supported by STAR*D	• Higher doses • Dizziness • Not widely used
High dose Venlafaxine	• Well-tolerated • Can be given in 1° care • NICE & STAR*D support	• Nausea and vomiting • Discontinuation reactions • May increase BP
ECT	• Effective, well established • Well supported	• Poor public reputation • Requires GA • Last line/Rapid response
Add Tri-iodothyronine	• Well tolerated • Literature support • BPD-D	• Clinical & biochemical TFT monitoring • Specialist referral • Expensive
Add Risperidone	• Small evidence base • Well-tolerated	• Hypotension • Hyperprolactinemia

Treatment Refractory Depression (3rd Line)

- Amantadine
- Buprenorphine
- Cabergoline
- D-cycloserine
- Pindolol
- Tianeptine
- Tryptophan
- Zinc
- Ziprasidone
- MAOI + TCA

Choosing between Switching or Adding an Adjunctive Medication

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
- There is more time to wait for a response (less severe, less functional impairment)
- Patient prefers to switch to another antidepressant

Choosing between Switching or Adding an Adjunctive Medication

Consider adding 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

Maintenance Treatment

- Primary aim: relapse prevention
- First episode: 6 to 9 months
- Multiple episodes: prolonged treatment, no data to suggest when to discontinue.
- Venlafaxine trial: 2 yr treatment better than 1 yr at relapse prevention
- Decision to discontinue: careful monitoring is required, particularly for the first 6 months

Maintenance Treatment

- Risk Factors to Consider Longer Term Maintenance Treatment with Antidepressants
  - Frequent, recurrent episodes
  - Severe episodes (psychosis, severe impairment, suicidality)
  - Chronic episodes
  - Presence of comorbid psychiatric or other medical conditions
  - Presence of residual symptoms
  - Difficult-to-treat episodes

Psychotic Depression

- TCAs are probably drugs of first choice in psychotic depression.
- SSRIs/SNRIs are a second-line alternative when TCAs are poorly tolerated.
- Augmentation of an antidepressant with olanzapine or quetiapine is recommended.
- The optimum dose and duration of antipsychotic augmentation are unknown
- Treatment is to be stopped during the maintenance phase, this should usually be the antipsychotic.
- ECT - rapid response/failure of other treatment

ECT in Depression

- Patients who have
  - failed medication trials,
  - have not tolerated medications,
  - have severe or psychotic symptoms,
  - are acutely suicidal or homicidal, or have marked symptoms of agitation or stupor.
- ECT is effective for depression in both major depressive disorder recent studies have indicated that major depressive episodes with psychotic features are no more responsive to ECT than nonpsychotic depressive disorders.

ECT in Depression

- Response rates to alternative treatments may be lower, while response to ECT in antidepressant nonresponders can be expected to be 50 to 70 percent.
- Elderly patients tend to respond to ECT more slowly than do young patients.

Other Treatment Options

- VNS
  - Left vagal nerve stimulation (VNS) using an electronic device implanted in the skin
  - Preliminary evidence of remission in chronic, recurrent major depressive disorder.
  - Mechanism is unknown
- Phototherapy
  - Bright light of 1,500 to 10,000 lux or more with light box before dawn
  - Seasonal affective disorder

Other Treatment Options

- rTMS
  - Focal secondary electrical stimulation of targeted cortical regions using short magnetic pulses.
  - It is nonconvulsive, requires no anesthesia, has a safe side effect profile
  - Indicated for the treatment of depression in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal e ective dose and duration in the current episode.

Other Treatment Options

- Sleep deprivation
  - Approximately 60 percent of patients with depressive disorders exhibit significant but transient benefits from total sleep deprivation.
  - Can augment pharmacotherapy, accelerate its response
  - Another method is phase delay/ partial sleep deprivation

Depression in Elderly

- Higher co-morbities
- Effective treatment of depression can improve mortality
- No anti-depressant completely safe
- SSRI, agomelatine, vortioxetine and duloxetine well tolerated
- Choice of anti-depressant needs to be individualized
- Effect on cognition debatable

Child and Adolescent Depression

- NICE and AACAP- psychological intervention first line in mild to moderate depression
- Moderate to severe depression- combined pharmacotherapy + psychotherapy
- US FDA approved- fluoxetine and escitalopram
- Black box warning- increased suicidal tendency with anti-depressants
- TCA and paroxetine not recommended
- Start low and go slow

Child and Adolescent Depression

	Drugs
1st line	• Fluoxetine (FDA approved for 8 years and over in the USA)
2nd line	• Sertraline/Citalopram
3rd line	• Escitalopram (FDA approved for 12 years and over in the USA)
4th line	• Consider augmentation of antidepressant with second-generation antipsychotic or lithium • Consider mirtazapine (where sedation required)

Depression in Pregnancy

- Patients already on AD and at risk of relapse- continue same drug
- Fresh episode:
  - History of previous response
  - Sertraline
- SSRI- increased risk of post-partum hemorrhage, PPH in neonate and discontinuation syndrome in newborn

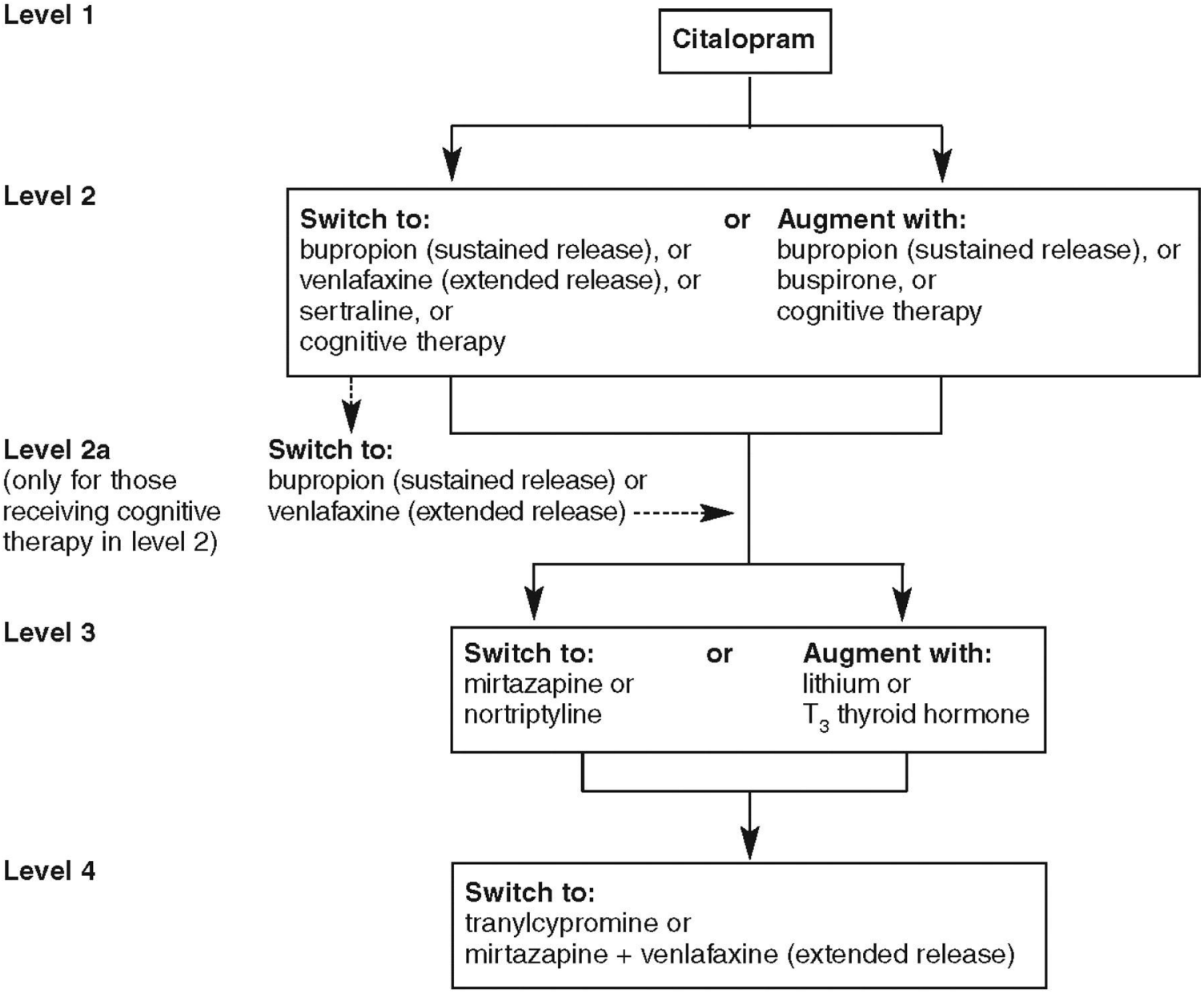
Specifiers/ Dimensions	Recommendations (Level of Evidence)	Comments
With anxious distress[a]	• Use an antidepressant with efficacy in generalized anxiety disorder (Level 4)	• No differences in efficacy between SSRIs, SNRIs, and bupropion (Level 2)
With catatonic features[a]	• Benzodiazepines (Level 3)	• 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) • 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) • Bupropion (Level 2) • Duloxetine (Level 2) • SSRIs (Level 2)[b] • Moclobemide (Level 3)	• Limited data available on cognitive effects of other antidepressants and on comparative differences in efficacy
With sleep disturbances	• Agomelatine (Level 1) • Mirtazapine (Level 2) • Quetiapine (Level 2) • 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) • Other SNRIs (pain) (Level 2) • Bupropion (fatigue) (Level 1) • SSRIs[b] (fatigue) (Level 2) • Duloxetine[b] (energy) (Level 2)	• Few antidepressants have been studied for somatic symptoms other than pain • Few comparative antidepressant studies for pain and other somatic symptoms

STAR*D Trial

- Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study is a large-scale clinical trial funded by the National Institutes of Health, aimed to develop and evaluate feasible treatment strategies to improve clinical outcomes for more representative, "real-world" outpatients with one or more prior failed treatments.
- Specifically, STAR*D aimed to determine which of several treatments are the most effective "next-step" treatments for patients whose symptoms do not remit or who cannot tolerate the initial treatment and, if needed, ensuing treatments.

Figure 1

STAR*D treatment levels



STAR*D Trial

- Remission rates lower than in clinical efficacy trials
- There is no clear medication "winner" for patients whose depression does not remit after one or more aggressive medication trials.
- Both switching and augmenting are reasonable options for patients after an initial antidepressant treatment has failed.

STAR*D Trial

- Medication trials of at least 8 wks with at least moderately aggressive dosing necessary for remission
- Pharmacologic differences between psychotropic medications do not translate into meaningful clinical differences, although tolerability differs
- CBT well tolerated, an option when anti-depressant trial fails

STAR*D Trial

- Common practice of selecting treatments based on symptom patterns has little empirical support
- The likelihood of remission after two vigorous medication trials substantially decreases. Thus an empirically supported definition for treatment-resistant depression seems to be two antidepressant failures.
- The finding that about two-thirds of patients may be expected to reach remission with up to four treatment attempts is encouraging for this disabling illness.

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