TACKLING LONG-TERM (ENDURING) DEPRESSION

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Enduring Depression

1. Chronic Depression/ Dysthymia/ Persistent Depression
2. Treatment Resistant Depression
3. Differential Diagnosis- other medical/SMU causes

Persistent Depressive Disorder (Dysthymia) ICD-10 300.4 (DSM-5 F34.1)

- This disorder represents a consolidation of DSM-IV-defined chronic major depressive disorder and dysthymic disorder.
- Depressed mood for most of the day, for more days than not, as indicated by either subjective account or observation by others, for at least 2 years.
- *Note:* In children and adolescents, mood can be irritable and duration must be at least 1 year.
- Presence, while depressed, of ***two (or more) of the following***:
  - Poor appetite or overeating.
  - Insomnia or hypersomnia.
  - Low energy or fatigue.
  - Low self-esteem.
  - Poor concentration or difficulty making decisions.
  - Feelings of hopelessness.
- During the ***2-year period*** (1 year for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 months at a time.
- Criteria for a major depressive disorder may be continuously present for 2 years.

NICE CG90
treatment of dysthymia/chronic depression

- **Antidepressants are NOT recommended for first-line treatment of recent-onset, mild depression (active monitoring, individual guided self-help, CBT or exercise)**
- Antidepressants recommended for treatment of moderate or severe depression **AND FOR DYSTHYMIA**
- Generic SSRI recommended as first line treatment (but watch for exacerbation of anxiety in the first 7-10 days)
- Inform all patients about withdrawal effects of stopping ADs
- Patients with at least 2 prior episodes should be treated for at least 2 years

DSM-5 Depression

Major Depressive Episode:

A ***Over the last 2 weeks, five of the following features*** should be present most of the day, or nearly every day (must include 1 or 2): 1. depressed mood
2. loss of interest or pleasure in almost all activities
3. significant weight loss or gain (more than 5% change in 1 month) or an increase or decrease in appetite nearly every day
4. insomnia or hypersomnia
5. psychomotor agitation or retardation (observable by others)
6. fatigue or loss of energy
7. feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach about being sick)
8. diminished ability to think or concentrate, or indecisiveness (either by subjective account or observation of others)
9. recurrent thoughts of death (not just fear of dying), or suicidal ideation, or a suicide attempt, or a specific plan for committing suicide.

B The symptoms cause clinically significant distress or impairment in functioning.
C The symptoms are not due to a medical/organic factor or illness.

Episodes are classified as mild (few symptoms beyond minimum, mild functional impairment), moderate (minimum symptoms and functional impairment between mild and severe), severe (most symptoms present, marked or greater functional impairment).

BAP CHRONIC DEPRESSION

- Lithium:
  - continue lithium in patients who needed lithium augmentation of antidepressants in acute treatment (B),
  - consider adding lithium to antidepressants in patients at high risk of relapse (B) or suicide (A),
  - do not routinely use lithium as monotherapy for relapse prevention but consider as a second-line alternative to antidepressants (B).
- CBT added to medication should be considered for
  - patients with residual symptoms (A) or at high risk of relapse (A).
  - In responders to acute-phase CBT, continuation medication is not routinely recommended (A); in unstable or partial remitters consider continuation CBT (B) or antidepressants (D).
  - IPT is not recommended as a sole continuation treatment for relapse prevention (A) unless acute response was to IPT monotherapy (C). Consider continuation IPT as an adjunct to antidepressants in patients with recurrent depression responding to acute-phase IPT combined with antidepressants (C).

Cleare, Pariante, Young et al (2015) BAP Depression Guidelines, Journal Psychopharmacol 29(5) 459–525

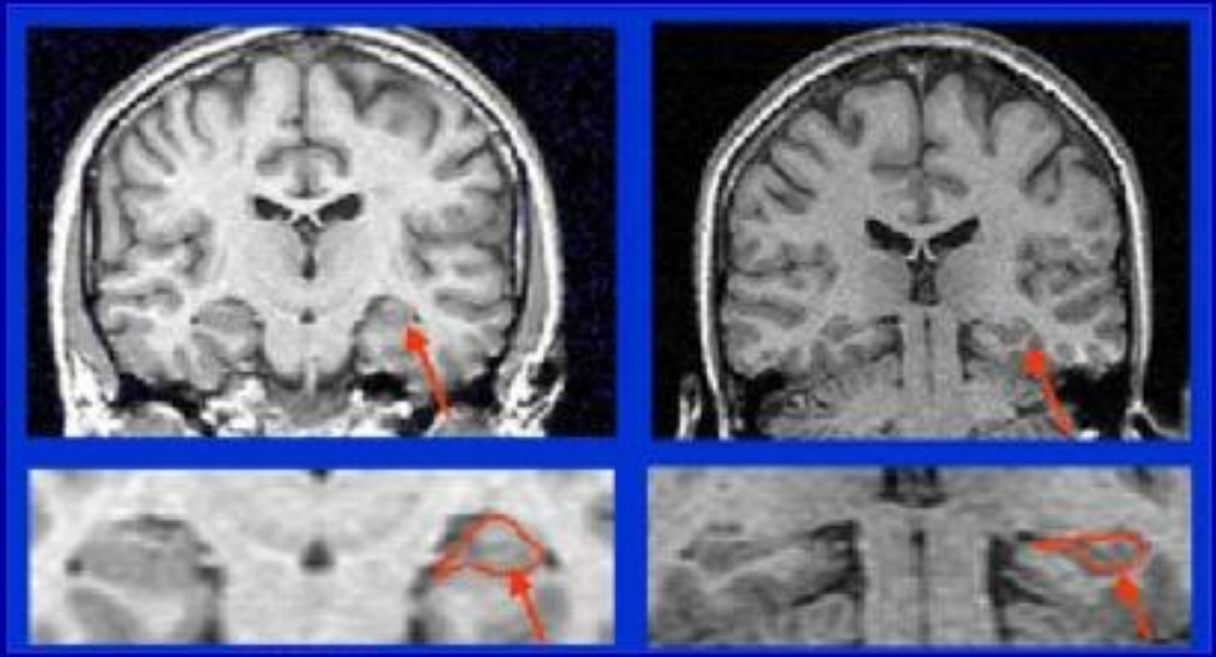
DSM-5 Depression: Persistent Depressive Disorder

- Identification of the severity and duration of depressive symptoms helps in the decision as to whether to prescribe antidepressants
- severity of depression commonly varies over time within individuals (Judd et al., 1998) so that decisions about prescribing antidepressants needs also to take into account individual history

Judd et al. (1998) *Arch Gen Psychiatry* 55: 694–700.

Brain Atrophy in Depression?

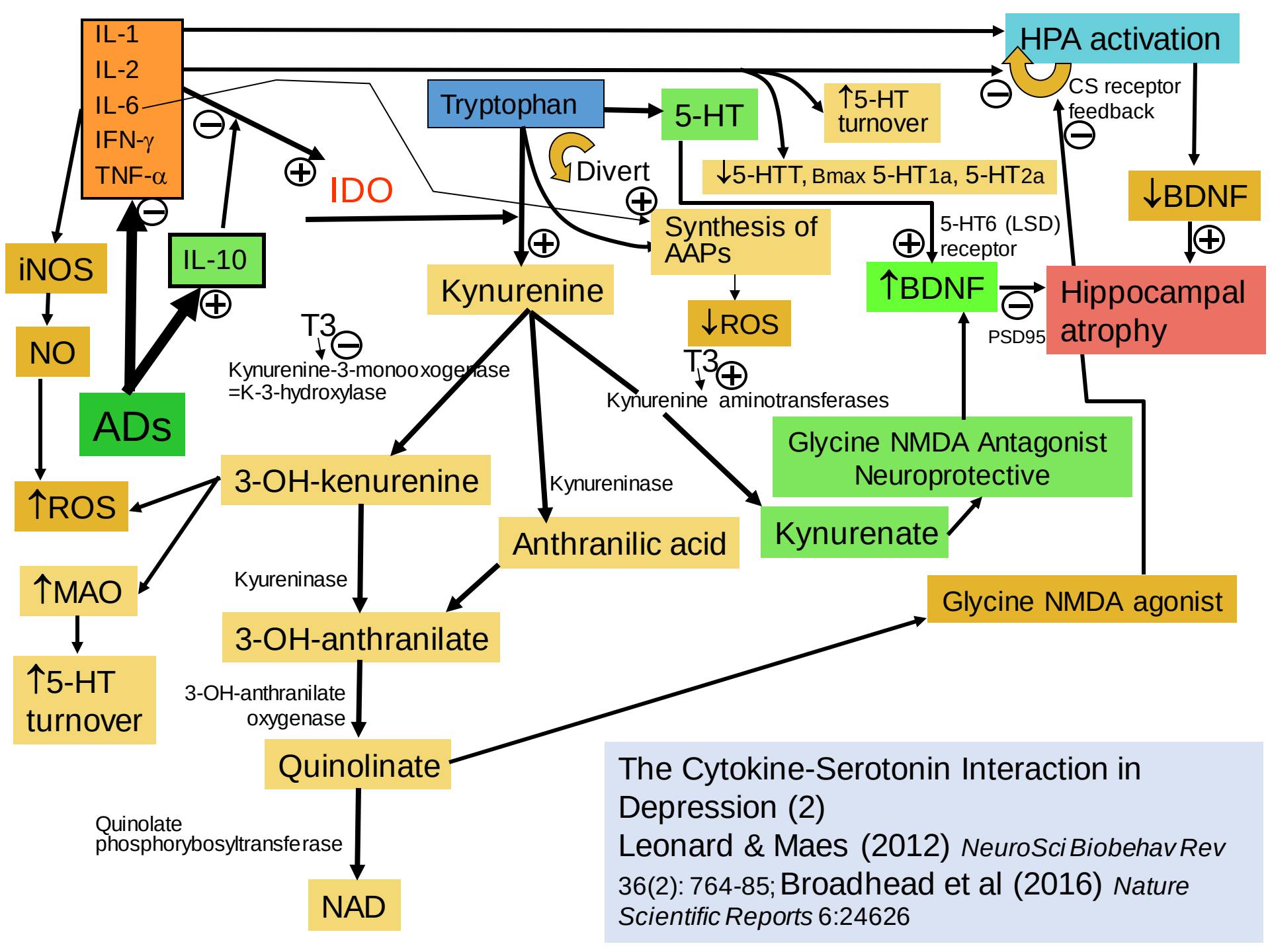
Atrophy of the Hippocampus in Depression



Normal Depression

Reprinted with permission from Bremner et al. *Am J Psychiatry* 2000

Bremner et al. *Am J Psychiatry* 2000;157(1):115-8.



The Cytokine-Serotonin Interaction in Depression (2)
Leonard & Maes (2012) *NeuroSci Biobehav Rev* 36(2): 764-85; Broadhead et al (2016) *Nature Scientific Reports* 6:24626

Treatment Resistant Depression

- **Definitions vary:**
- Failure to respond to at least 1 (usually 2 or more) antidepressant treatments given at an adequate dose, adequate duration, with good patient adherence
- **Prevalence:**
- Primary care 45% non-responders after 6m treatment[1]
- Secondary care meta-analysis 46% non-responders[2]
- STAR*D 70% non-responders after 12 weeks Rx 1 drug, 70-80% non-responders after second drug[3]
- For Treatment Options see:
  - Taylor et al The Maudsley Prescribing Guidelines in Psychiatry. 13th Edition. Wiley Blackwell (2018) pp 254-267
  - British Association of Psychopharmacology Depression Guidelines. J Psychopharmacology (2015) 29(5): 459–525

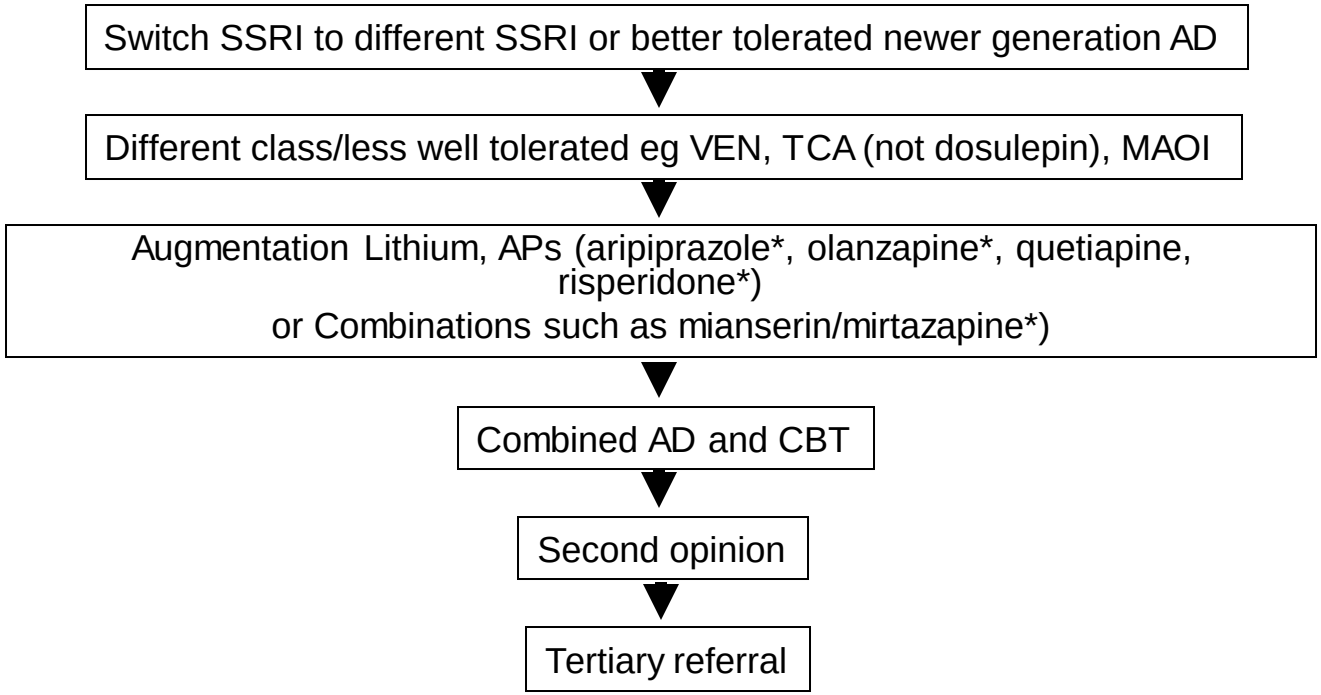
1. Corey-Lisle et al (2004). Arch Intern Med. 2004;164:1197-1204
2. Papakostas & Fava (2006);. Neuropsychopharmacology. 31:s158.
3. Trivedi et al. (2006) Am J Psychiatry.163:28-40

Treatment Resistant Depression

- ***Specialist services***
- Management of more complex or treatment-resistant cases of depression can benefit from referral to practitioners with special expertise in affective disorders or tertiary centres of excellence, a practice recommended by NICE[1]
- One study of inpatient treatment on a tertiary unit for affective disorders found response rates of 69% in a group of previously highly treatment-resistant patients[2]
- Multiple Therapy Resistant cases managed in specialist centres described by McAllister-Williams[3]

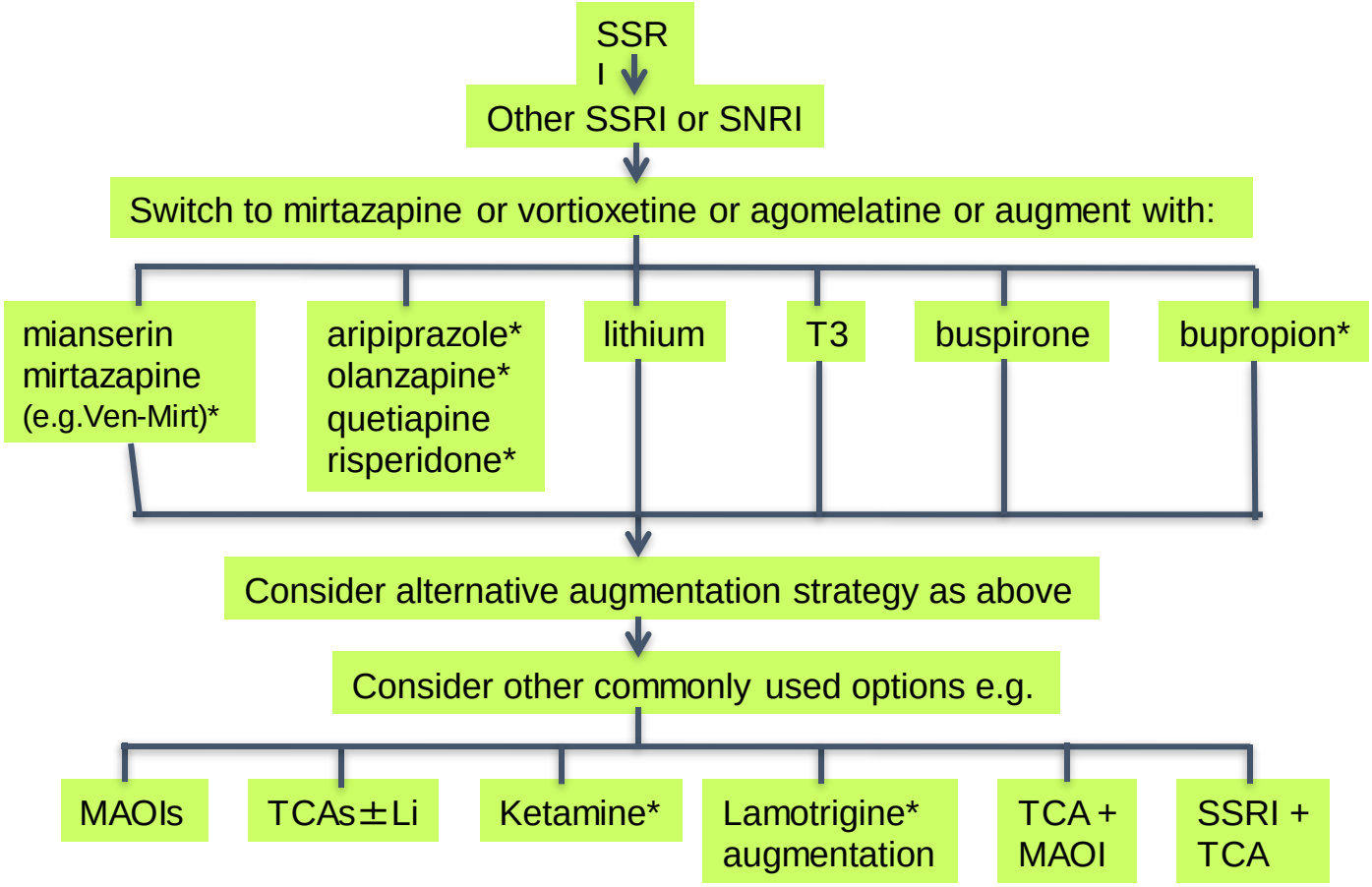
1. Shepherd DJ, Insole LJ, McAllister-Williams RH, et al. (2009) *The Psychiatrist* 33:41–43.
2. Wooderson SC, Juruena MF, Fekadu A, et al. (2011) *J Affect Disord* 131: 92–103.
3. McAllister-Williams et al (2018) BJPsych doi: 10.1192/bjp.2017.33

NICE: Suggested TRD treatment pathway (CG90) 2009/2016



UPDATE NOW NOT EXPECTED UNTIL LATE 2019 FOLLOWING FAILUER TO AGREE 3 DRAFTS 2017-2018

Maudsley Treatment Guidelines



Taylor D, Barnes T, Young A. Maudsley Prescribing Guidelines in Psychiatry - 13th Edition. Oxford, UK: Wiley-Blackwell 2018.

BAP Guidelines 2015
Most detailed & evidence based UK guidelines

BAP Guidelines

Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines

Anthony Cleare[1], CM Pariante[2] and AH Young[3]
With expert co-authors (in alphabetical order):
IM Anderson[4], D Christmas[5], PJ Cowen[6], C Dickens[7], IN Ferrier[8], J Geddes[9], S Gilbody[10], PM Haddad[11], C Katona[12], G Lewis[12], A Malizia[13], RH McAllister-Williams[14], P Ramchandani[15], J Scott[16], D Taylor[17], R Uher[18] and the members of the Consensus Meeting[19]
Endorsed by the British Association for Psychopharmacology

Psychopharm

Journal of Psychopharmacology
2015, Vol. 29(5) 459–525

DOI: 10.1177/0269881115581093
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BAP 2015 options after failure of initial AD

1. Dose increase
2. Different class of AD e.g. those with evidence of higher efficacy
3. Clomipramine, venlafaxine≥150mg/d, escitalopram 20mg/d, sertraline, amitriptyline, mirtazapine
4. Augment with (first line) - quetiapine, aripiprazole*, lithium: (second line) - risperidone*, olanzapine*, T3, mirtazapine*
5. Augment with (third line)* – bupropion, buspirone, lamotrigine, LTP, modafanil, stimulants, oestrogen, testosterone. Venlafaxine-selegiline combo in elderly
6. ECT, tDCS, rTMS, VNS, DBS, PSYCHOSURGERY
7. Ω3FA,SAMe, l-methyl folate, exercise

* Not licenced in the UK for depression

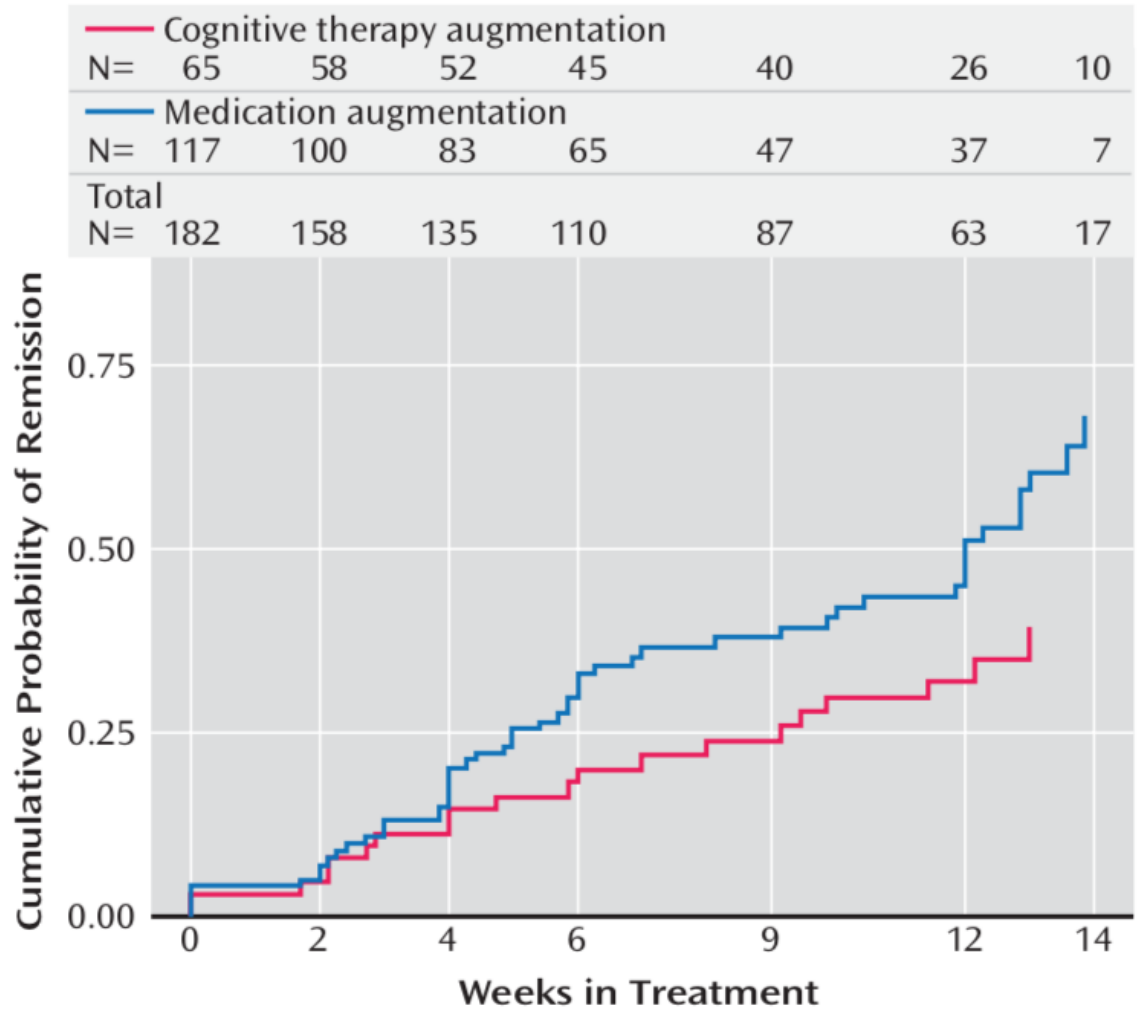
Cleare et al 2015 BAP Guidelines J Psychopharmacol 29(5): 459-526

P Fonagy, F Rost, J Carlyle, S McPherson, R Thomas, R M Pasco Fearon, D Goldberg, D Taylor:
Pragmatic randomized controlled trial of long-term psychoanalytic psychotherapy for treatment-resistant depression: the Tavistock Adult Depression Study (TADS)
World Psychiatry (2015)
https://onlinelibrary.wiley.com/doi/full/10.1002/wps.20267

- "Complete remission was infrequent in both groups at the end of treatment (9.4% in the LTPP group vs. 6.5% in the control group) as well as at 42-month follow-up (14.9% vs. 4.4%).
- Partial remission was not significantly more likely in the LTPP than in the control group at the end of treatment (32.1% vs. 23.9%, p=0.37), but ***significant differences emerged during follow-up (24 months: 38.8% vs. 19.2%, p=0.03; 30 months: 34.7% vs. 12.2%, p=0.008; 42 months: 30.0% vs. 4.4%, p=0.001)***

- Cost and hence affordability for the NHS?

Time to Remission and Cumulative Probability of Remission for STAR*D Level 2 TRD Participants Receiving Augmentation Treatments, by Treatment Option[a]



[a] Log-rank=5.2124, p=0.0224.

Non-responders to initial high dose citalopram for 14 weeks.
Medication Switch to bupropion SR, or venlafaxine, OR switch to CBT,
OR
augmentation of initial citalopram with bupropion SR, buspirone OR CBT

CBT up to 16 sessions

Thase et al (2007) Am J Psychiatry 164(5): 739-752

Differential Diagnosis of Depression:

- Other Psychiatric Diagnoses
  - Dysthymia, bipolar Disorder, anxiety disorders, eating disorder, schizophrenia (negative symptoms), personality disorders

- Neurological Disorders
  - Dementia, Parkinson's Disease, Huntington's disease, MS, stroke, epilepsy

- Endocrine Disorders
  - Addison's disease, Cushing's disease, hyper/hypothyroidism, menopausal symptoms, hyperparathyroidism, hypopituitarism

- Metabolic disorders: Hypoglycaemia, hypercalcaemia, porphyria.
- Infections: Syphilis, Lyme disease, HIV encephalopathy
- Sleep disorders: especially sleep apnoea

- Medication related
  - Antihypertensives (beta-blockers, methyldopa, calcium channel blockers); steroids; chemotherapy agents (e.g. vincristine, interferon, Chimeric Monoclonal antibody Infleximab amphotericin B, vinblastine, medicines that affect sex hormones (oestrogen, progesterone, testosterone); and psychiatric medication (esp older antipsychotics)

  - Substance Misuse (alcohol, benzodiazepines, opiates, cannabis/SPICE, cocaine, amfetamines.

Conclusions and Questions

- Differentiate mild from moderate to severe depression
- Antidepressants not indicated for mild/subsyndromal depression
- Treatment of Major Depression remains sub-optimal
- Few specific drugs indicated for TRD[1] (fail on 2 different drugs class)
- Any logical sequence for augmentation of ADs post STAR∗D?
- Is omitting SNRIs for TRD reasonable (NICE GDG 2017-18)?
- What rank ordering choice is appropriate from meta-analysis (mirtazepine, escitalopram, agomelatine, vortioxetine, duloxetine)? Valid only for non-TRD?
- Does the evidence justify vortioxetine's NICE recommended "position"?
- Specialist TRD/Mood clinics appropriate to manage complex TRD
- Arrival of intra-nasal esketamine in October 2019

1. Reference for original definition diagnosis and definition of treatment-resistant depression. Fava M. Biol Psychiatry. 2003 Apr 15; 53(8):649-59.