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Antidepressant Prescribing: The important bits

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Why is depression THE most important disorder to know how to treat?

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Depression increases morbidity and mortality from common physical disease

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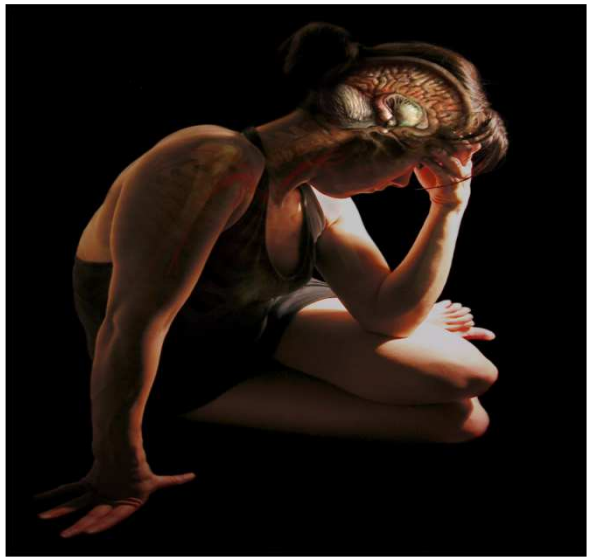
39% increase in mortality in **cancer** patients diagnosed with depression.[1]



COPD – depressive symptoms almost double the risk of mortality.[2]

Depression associated with 60% increased risk for **CHD**[6] and 2X risk of death in CHD patients with depression.[7]

Depression associated with 60% increased risk of developing **diabetes**[3], increased mortality[4]

COPD = chronic obstructive pulmonary disease
CHD = coronary heart disease

1. Satin JR *Cancer* 2009;115: 5349-5361 2. de Voogd JN et al. *Chest* 2009;135:619-625
3. Mezuk B et al. *Diabetes care* 2008; 31:2383-2390 4. Katon W et al. *J Gen Inern Med* 2008;23:1571-1575
6. Wulsin LR and Singal BM. *Psychosomatic Medicine* 2003;65:201-10
7. Barth J et al. *Psychosomatic Medicine* 2004;:66:802-13

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Impact of depression on benefit claims (2010)

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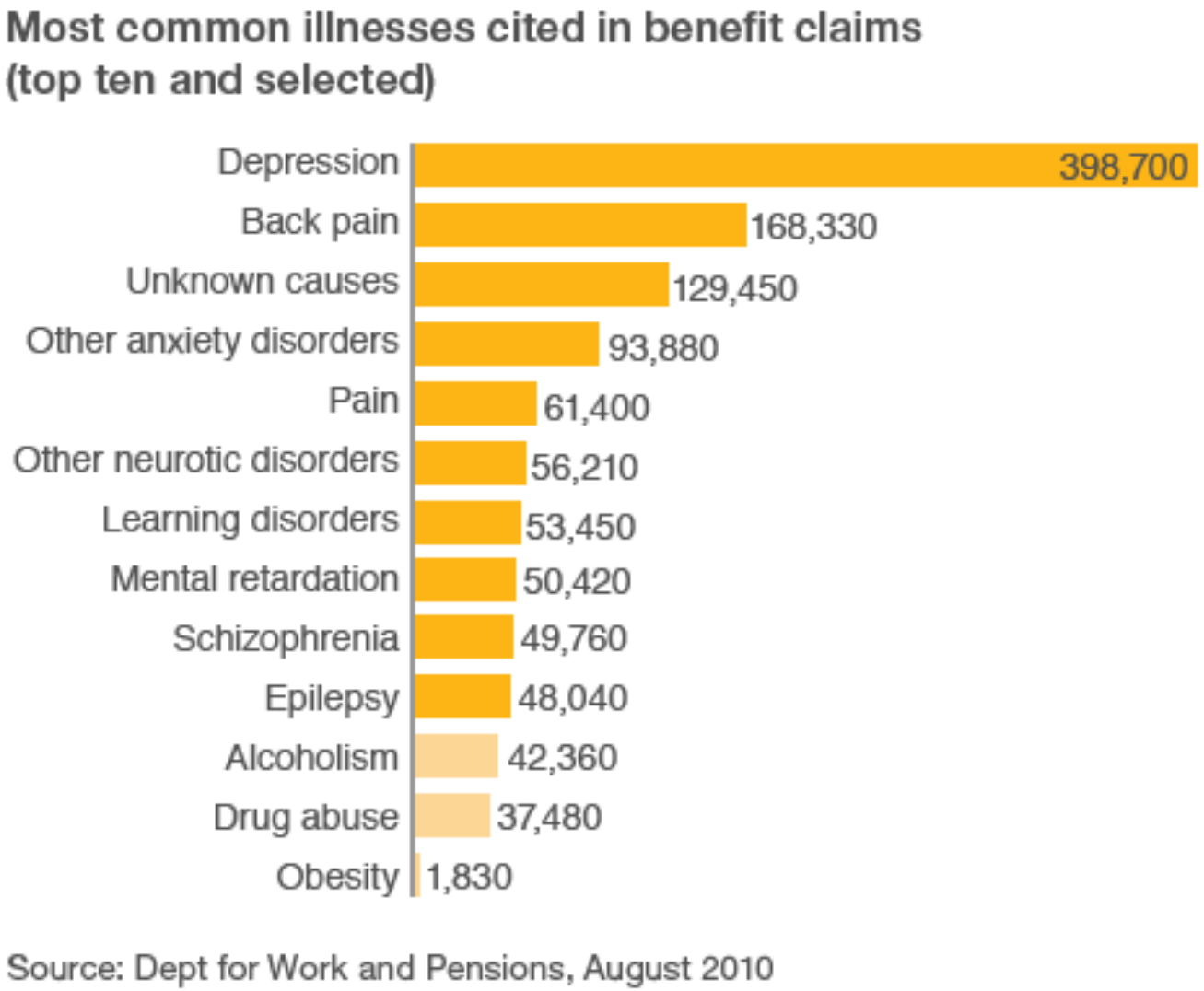

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Depression: Some key questions

- Who should be treated?
- Treatment: what and how?
- ……and then what?

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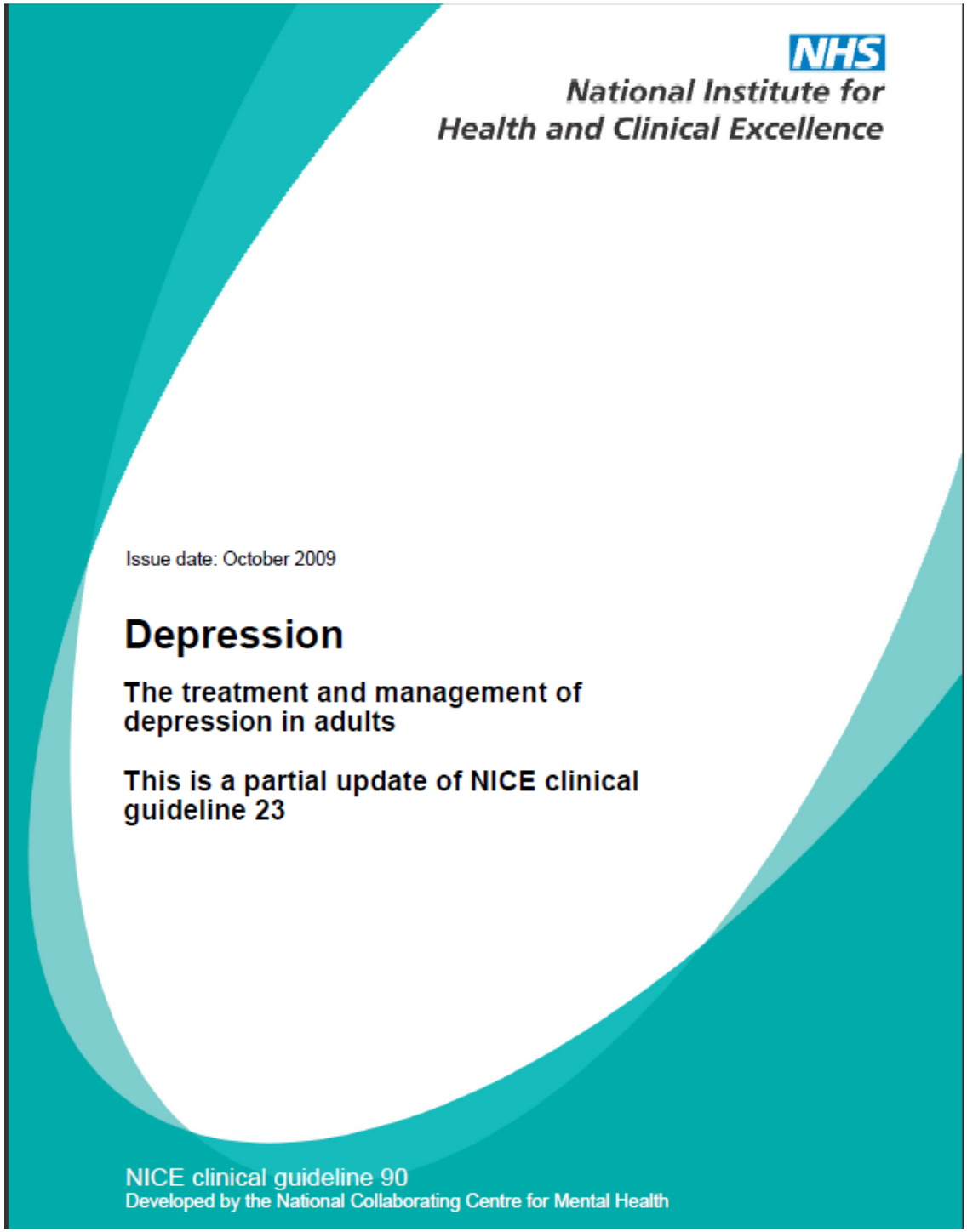

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Psychopharm

Journal of Psychopharmacology
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Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2000 British Association for Psychopharmacology guidelines

IM Anderson *Senior Lecturer and Honorary Consultant Psychiatrist, Neuroscience and Psychiatry Unit, University of Manchester, UK.*

IN Ferrier *Professor of Psychiatry, Honorary Consultant Psychiatrist, School of Neurology, Neurobiology and Psychiatry, Newcastle University, Royal Victoria Infirmary, Newcastle upon Tyne, UK.*

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PJ Cowen *Professor of Psychopharmacology, The Psychopharmacology Research Unit, University Department of Psychiatry, Warneford Hospital, Oxford, UK.*

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A Tylee *Professor of Primary Care Mental Health, NIHR Biomedical Research Centre and Health Services and Population Research Department, Institute of Psychiatry, Kings College London, London, UK.*

Rules of thumb

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Emphasis on issue of importance to day to day practice

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Depression: Some key questions

- Who should be treated?
- Treatment: what and how?
- …and then what?

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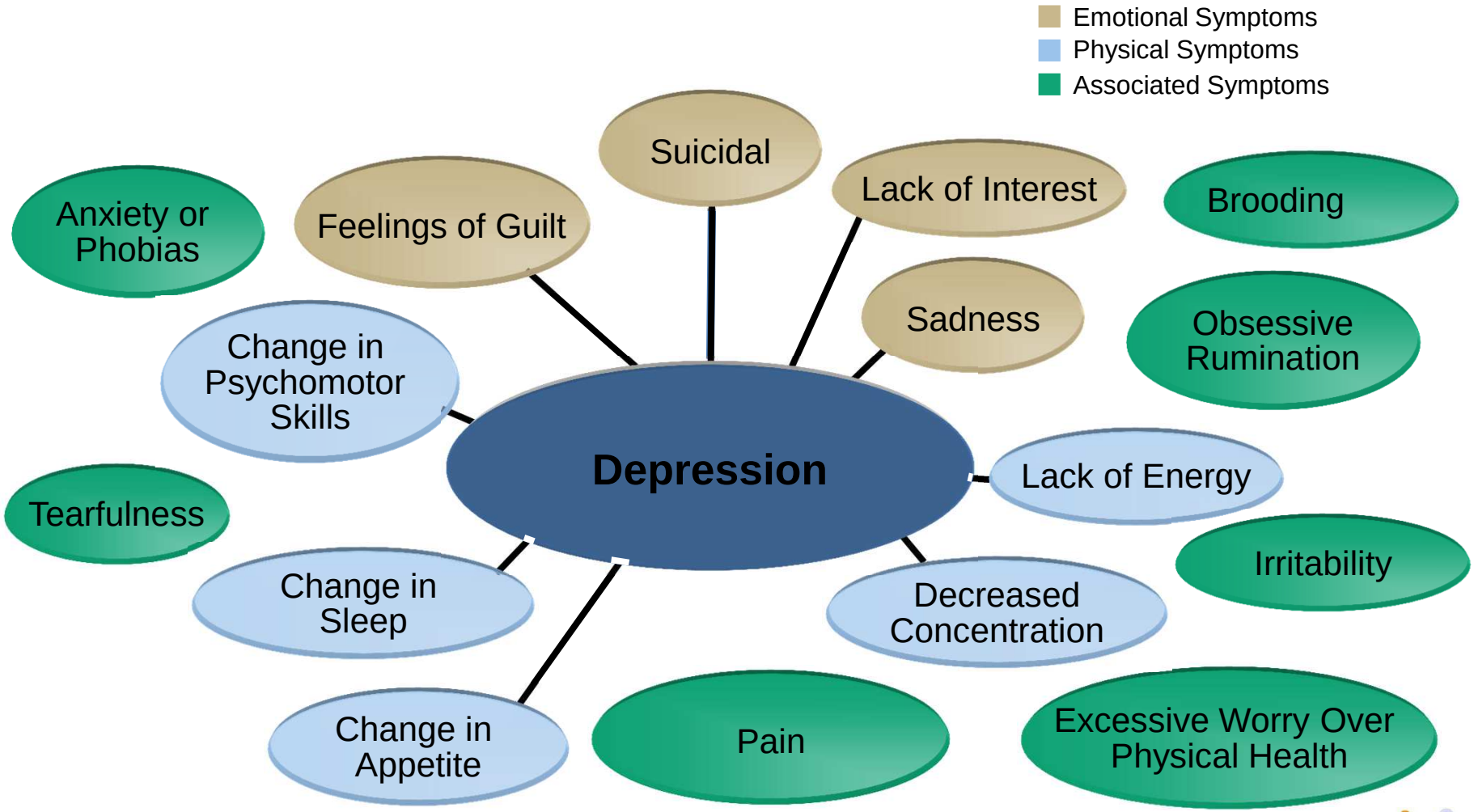
Diagnostic Dilemmas/Issues

1. Differentiating normal human misery from depressive illness

Depression is a complex syndrome



APA. *DSM-IV-TR*; 2000:352,356.

Diagnosis of Depression

DSM-IV Criteria – as recommended by NICE

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- **5 or more** of the following over a two week period:
  - *depressed mood
  - *markedly diminished interest or pleasure in all activities
  - weight loss, decreased or increased appetite
  - insomnia or hypersomnia
  - psychomotor agitation or retardation
  - fatigue or loss of energy
  - feelings of worthlessness or inappropriate guilt
  - diminished ability to think or concentrate
  - recurrent thoughts of death or suicide

  - N.B. must have one of symptoms marked with *
  - Must be associated with impairment of function

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Diagnosis – a pitfall

Big rule of thumb!!

- NOTE – It does not matter how **understandable** the depression is. If it meets criteria, **then it is depression**

Diagnostic Dilemmas/Issues

1. Differentiating normal human misery from depressive illness
2. Differentiating bipolar disorder from unipolar

Bipolar disorder

- Bipolar disorder often does not respond to antidepressants and may be made worse by them. It is vital to identify it.

Big rule of thumb!!

- **With every new presentation of a depressive episode, ALWAYS ask about symptoms of elevated mood**
  - (elation, racing thoughts, lack of need for sleep, increased activity etc)

Indications for antidepressants: Duration and severity of depression guides treatment choice (BAP guidelines)

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- Antidepressants are a first line treatment for:
  - moderate and severe MDD in adults,
  - Sub-threshold depression that has persisted for 2 years or more.

- Antidepressants are an option for mild MDD in adults especially if:
  - there is a history of moderate to severe recurrent depression
  - the depression has persisted for more than 2–3 months

- Antidepressants are not a first line treatment for short duration sub-threshold depression in adults but consider if:
  - there is a prior history of moderate to severe recurrent depression
  - the depression persists for more than 2–3 months

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Depression: Some key questions

- Who should be treated?
- Treatment: what and how?
- ……and then what?

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Correlation Between Hippocampal Volume and Duration of Untreated Depression*

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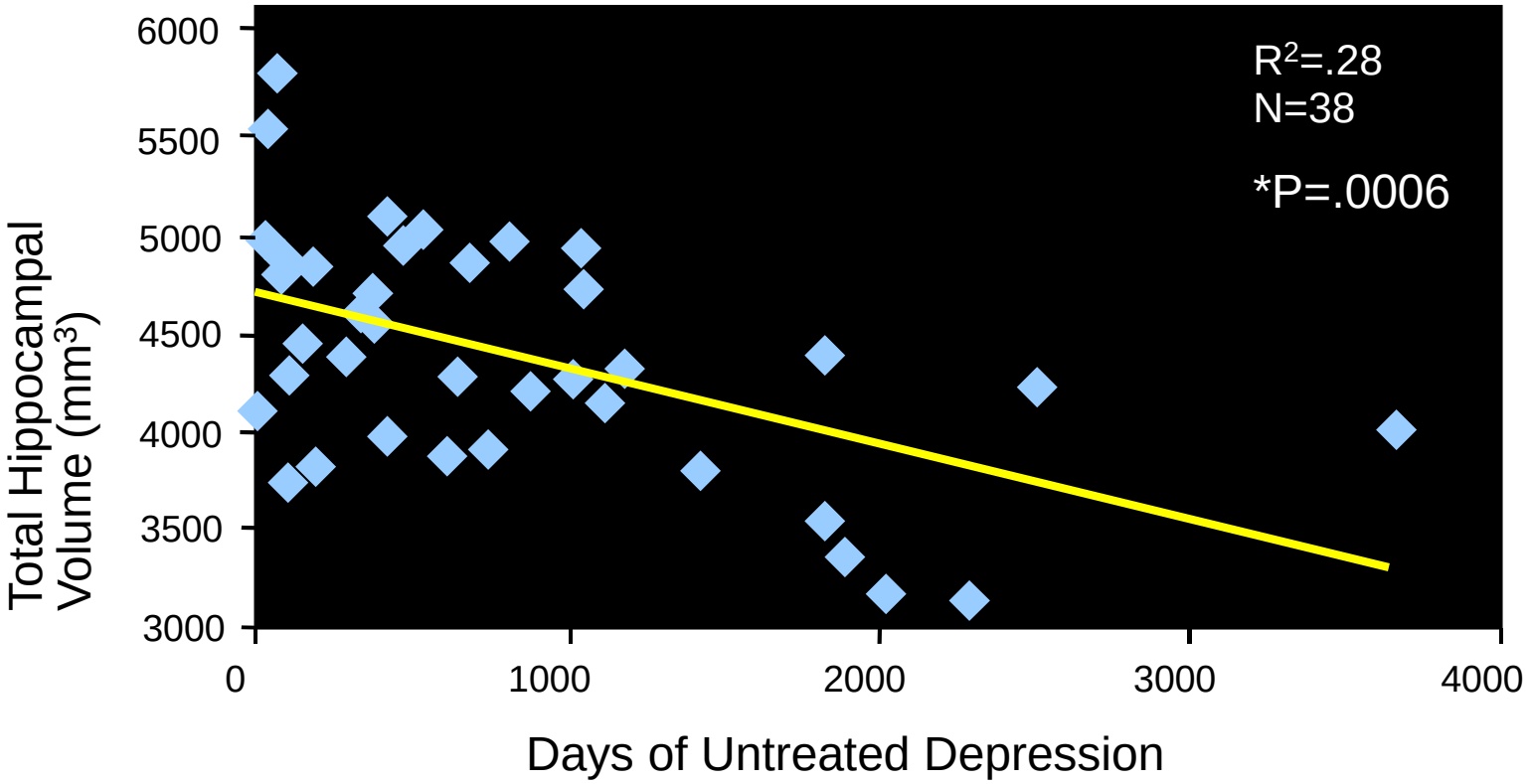
Female Outpatients With Recurrent Depression in Remission



* Significant inverse relationship between total hippocampal volume and the length of time depression went untreated.

Sheline YI, et al. *Am J Psychiatry* 2003;160(8):1516-1518.

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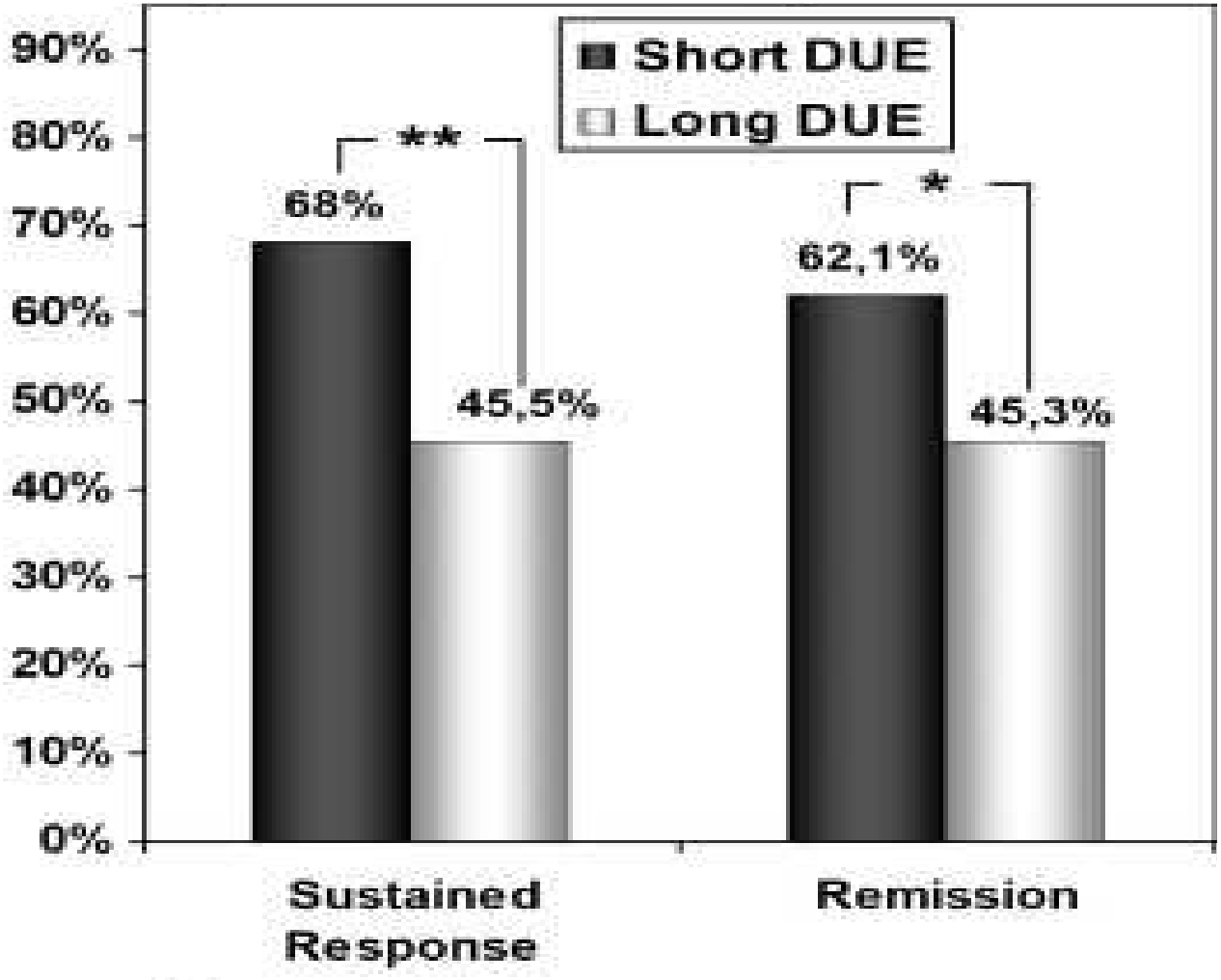
Effect of duration of un-treated depression on response and remission



De Diego-Adelino et al. (2010) J Affect Disorders 120:221 - 225

Algorithm (ALGO) vs treatment as usual (TAU)

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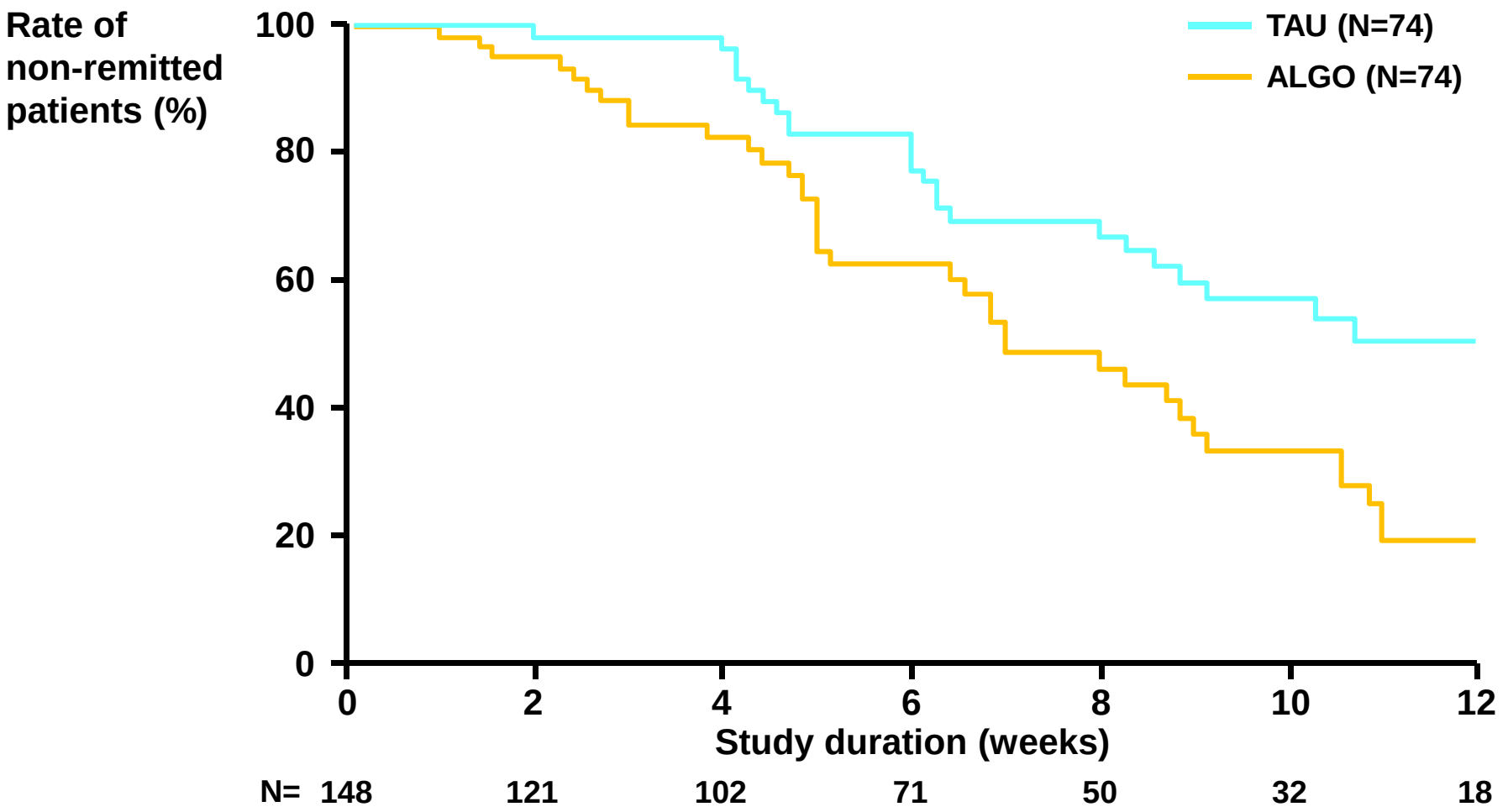

HR=2.0 (p=0.004)
Survival analysis (ITT group)

Bauer et al. *J Clin Psychopharmacol* 2009;29:327

Principles of treatment of depression

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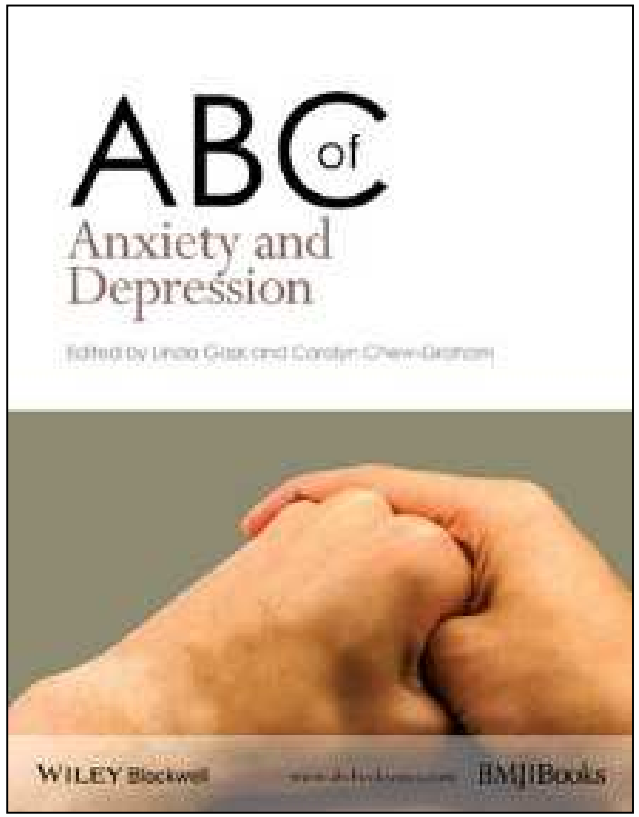
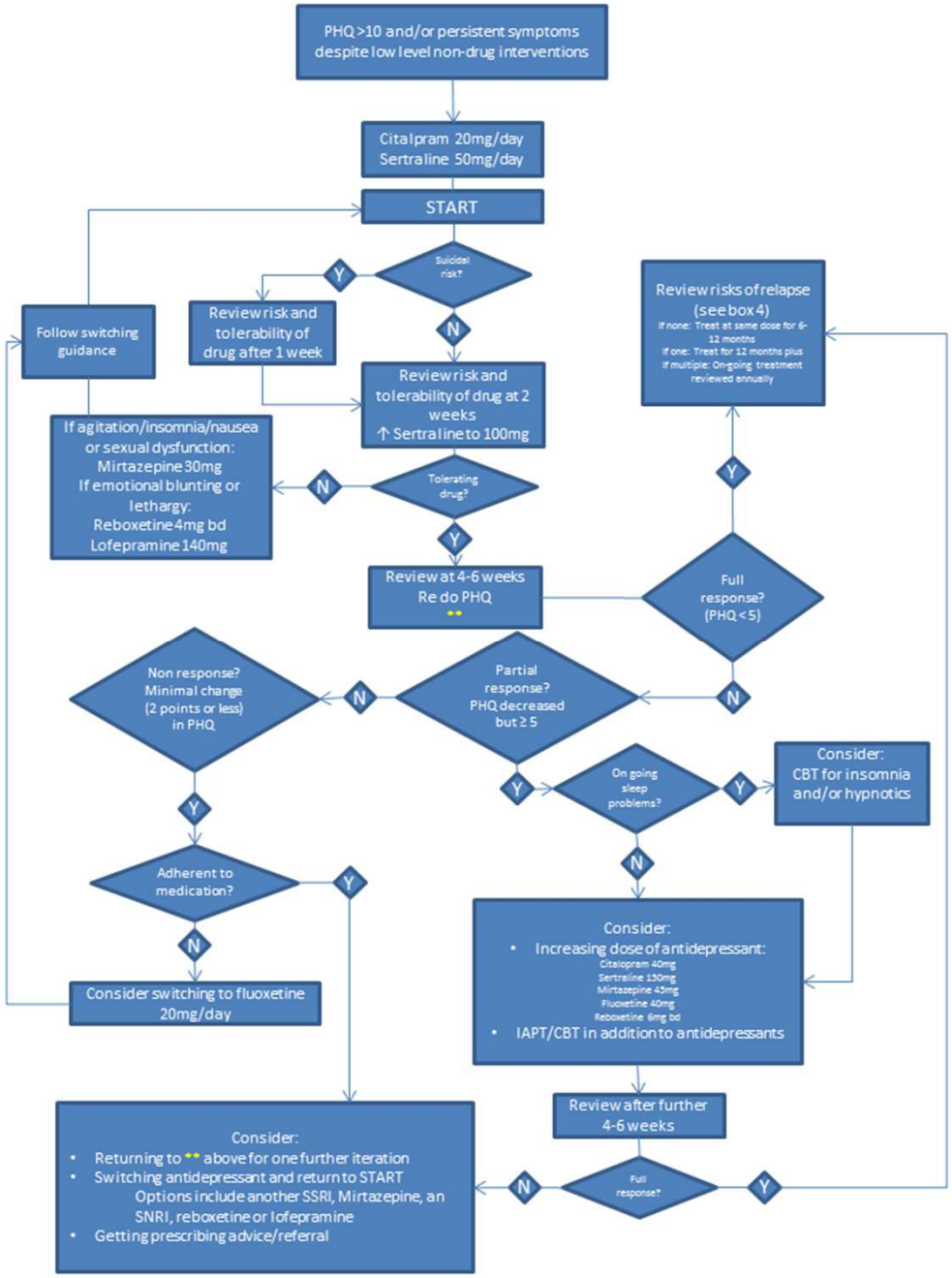
Rule of thumb!!

- **Don't waste too much time before treating patients**
  - If you do it damages their brains and makes them less likely to respond
- **Be systematic in how you treat patients**
  - Your plan should include critical decision points:
    - At a specific point in time if X then do 1; if Y do 2.

An algorithm

McAllister-Williams & Yates (2014) in "ABC of Anxiety and Depression" Gask and Chew-Graham, Wiley





Getting started

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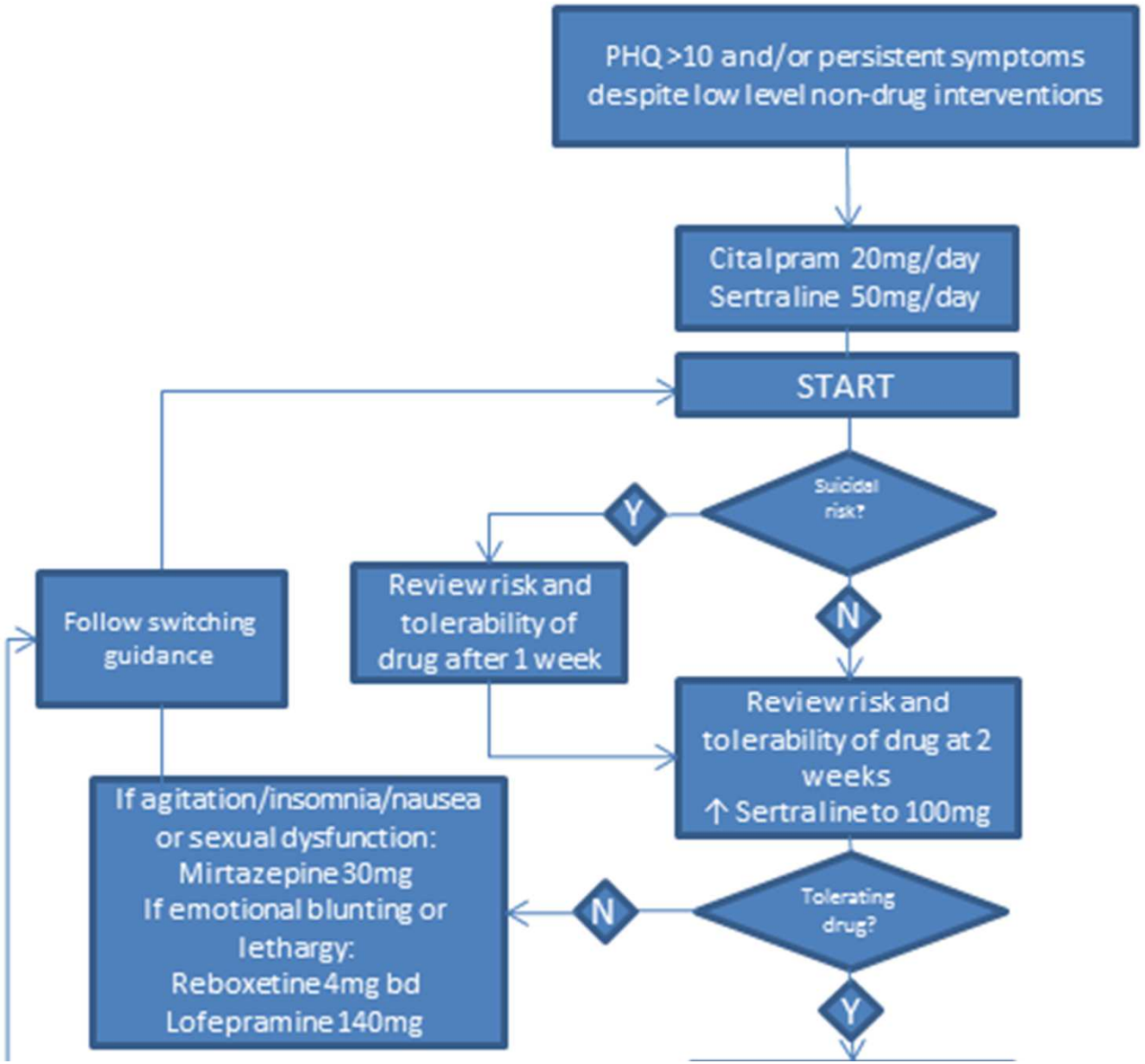

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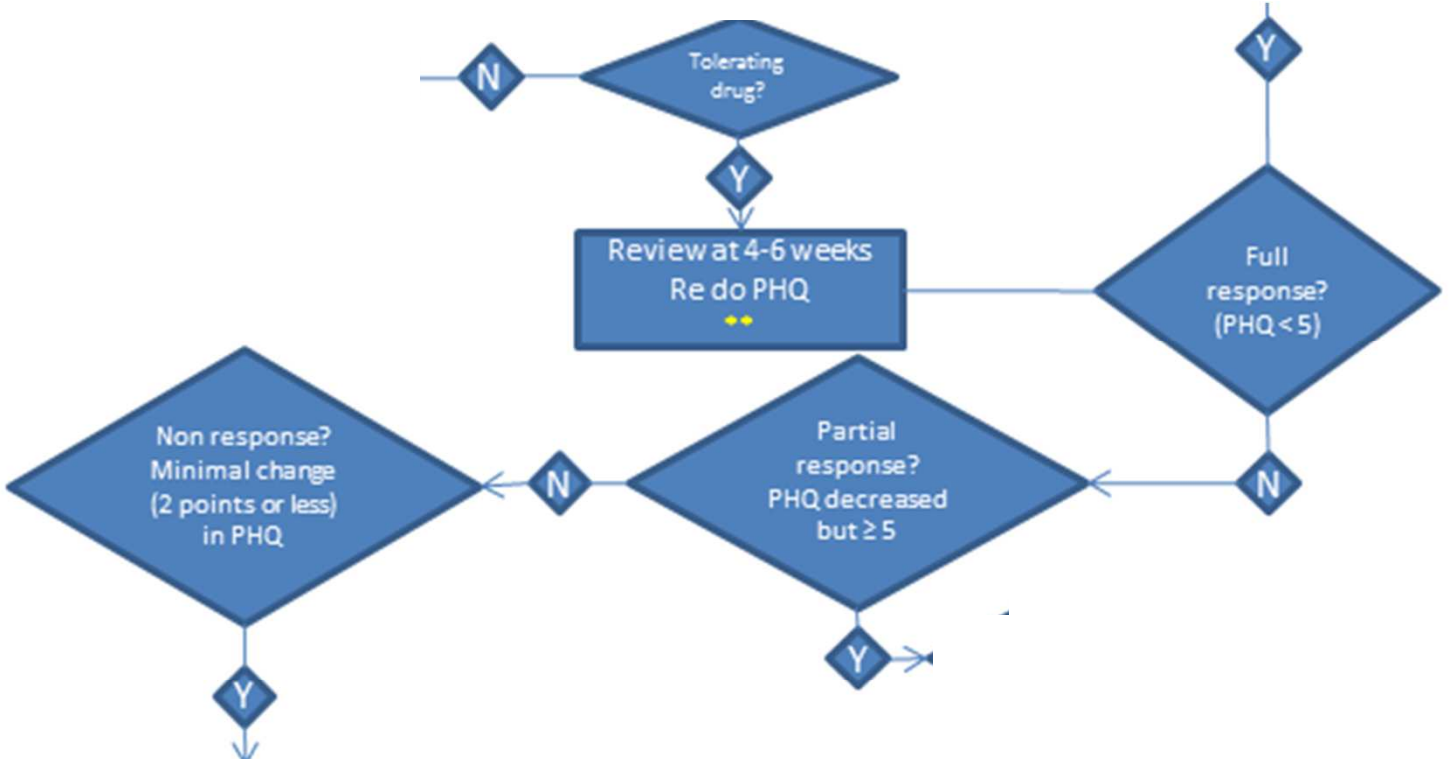
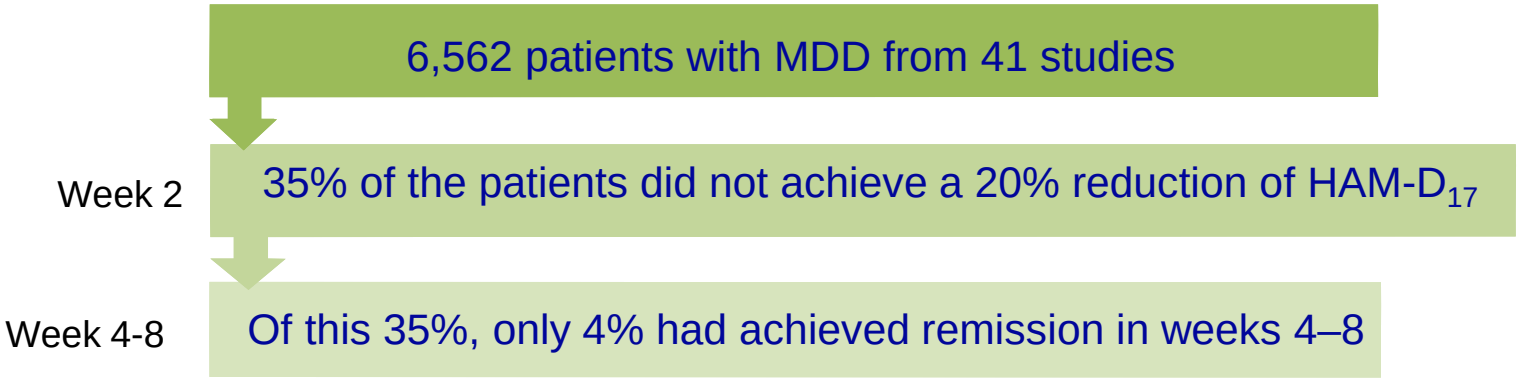
Assessing response



Lack of early response predicts failure to achieve remission

Meta-analysis of 41 studies of TCAs, mirtazapine, SSRIs, venlafaxine, etc. (6,562 patients)[1]



Conclusion:

- Lack of improvement during the first two weeks (≤20% decrease in HAM-D_{17}) of treatment may indicate that changes in depression management should be considered earlier than conventionally thought

1. Szegedi A, et al. *J Clin Psych* 2009;70:344–53.

Incomplete remission associated with chronic impairment in functioning

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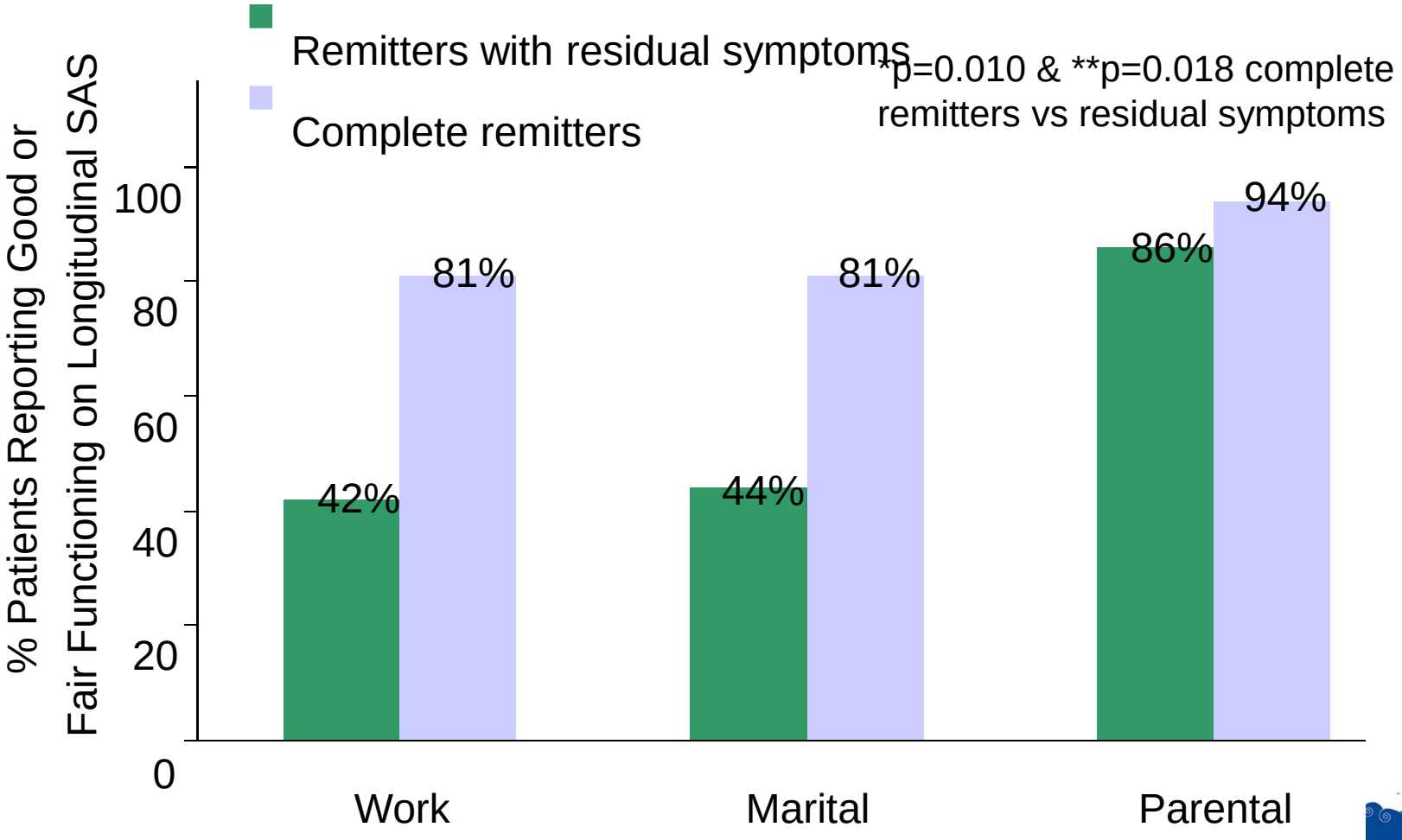

Kennedy N and Paykel ES. *J Affect Disord* 2004;80:135–44.

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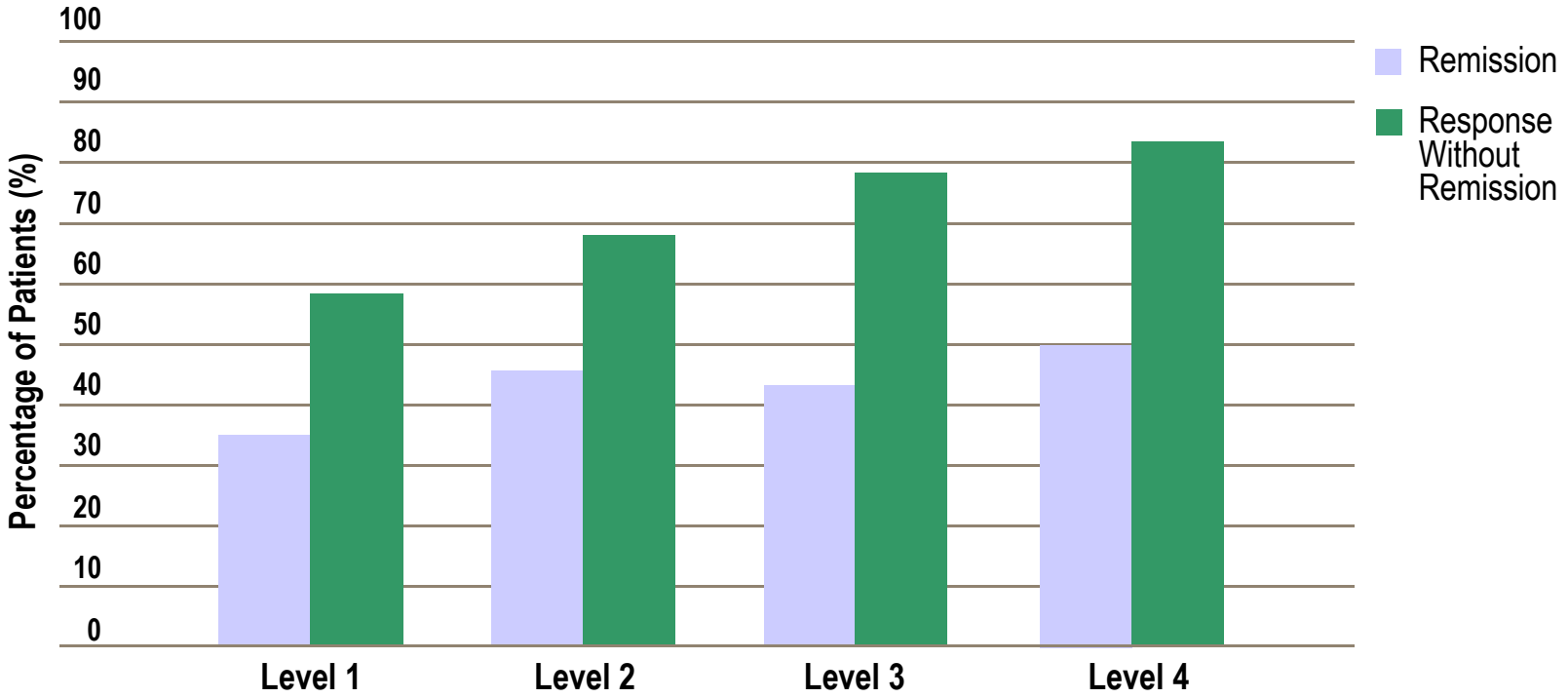
STAR*D: Failure to achieve remission increases the risk of relapse



Remission is defined as QIDS-SR_{16} ≤ 5 and response is defined as ≥ 50% improvement of QIDS-SR_{16} after 12–14 weeks of acute treatment in level 1, 2, 3 or 4. The relapse rate was examined over 12 months of naturalistic treatment.

Rush AJ, et al. *Am J Psychiatry* 2006;163(11):1905–17.

Assessing response

Rule of thumb!!

- **Assess response systematically**
- **Review response after 4-6 weeks**
  - After 2-4 weeks there should be at least some response; 4-6 weeks there should be significant response (add 1-2 weeks if elderly)
- **Assess for response, partial response and no response**
  - Partial response is associated with impaired social functioning and increased risk of relapse

Dealing with partial response

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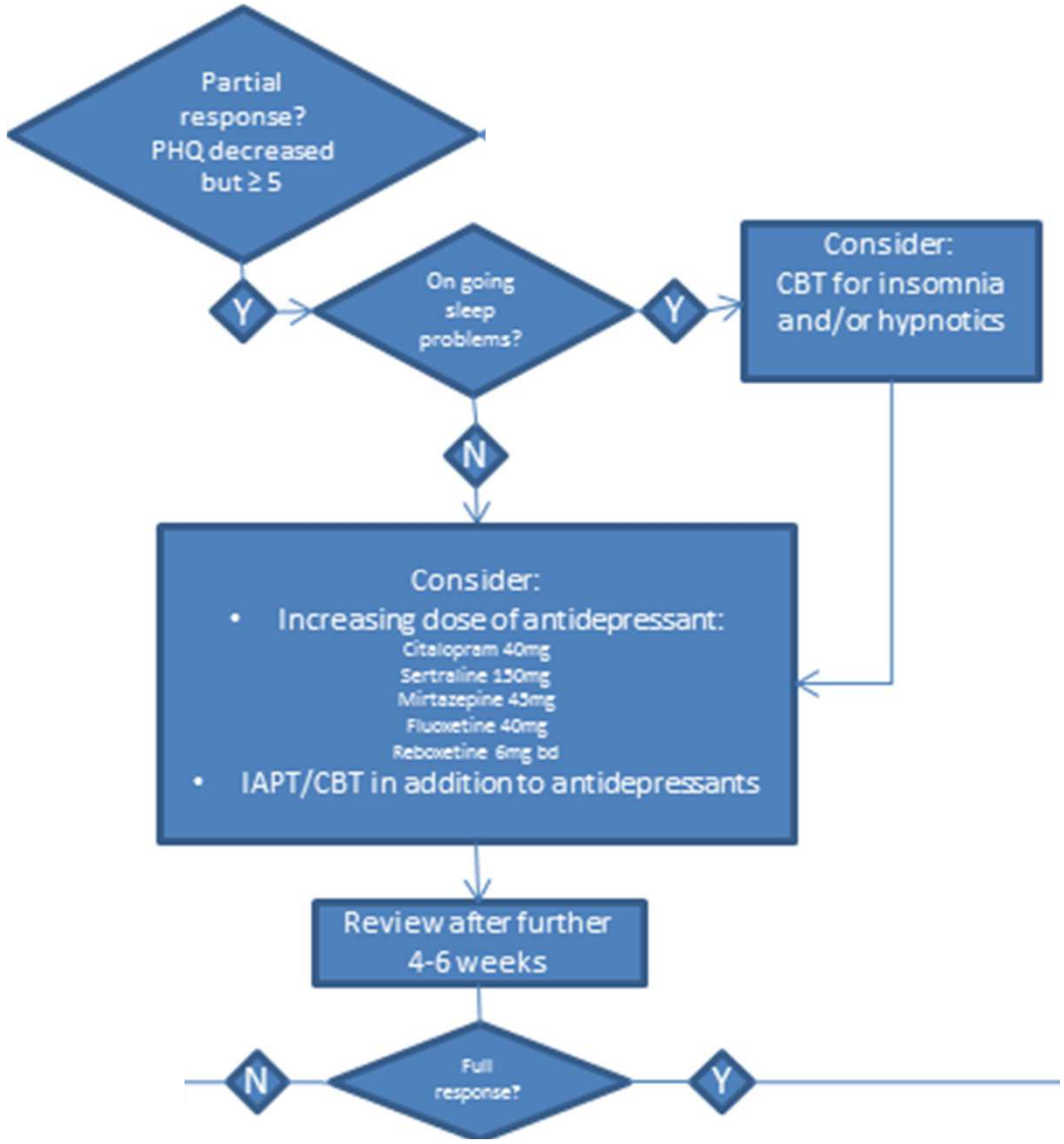

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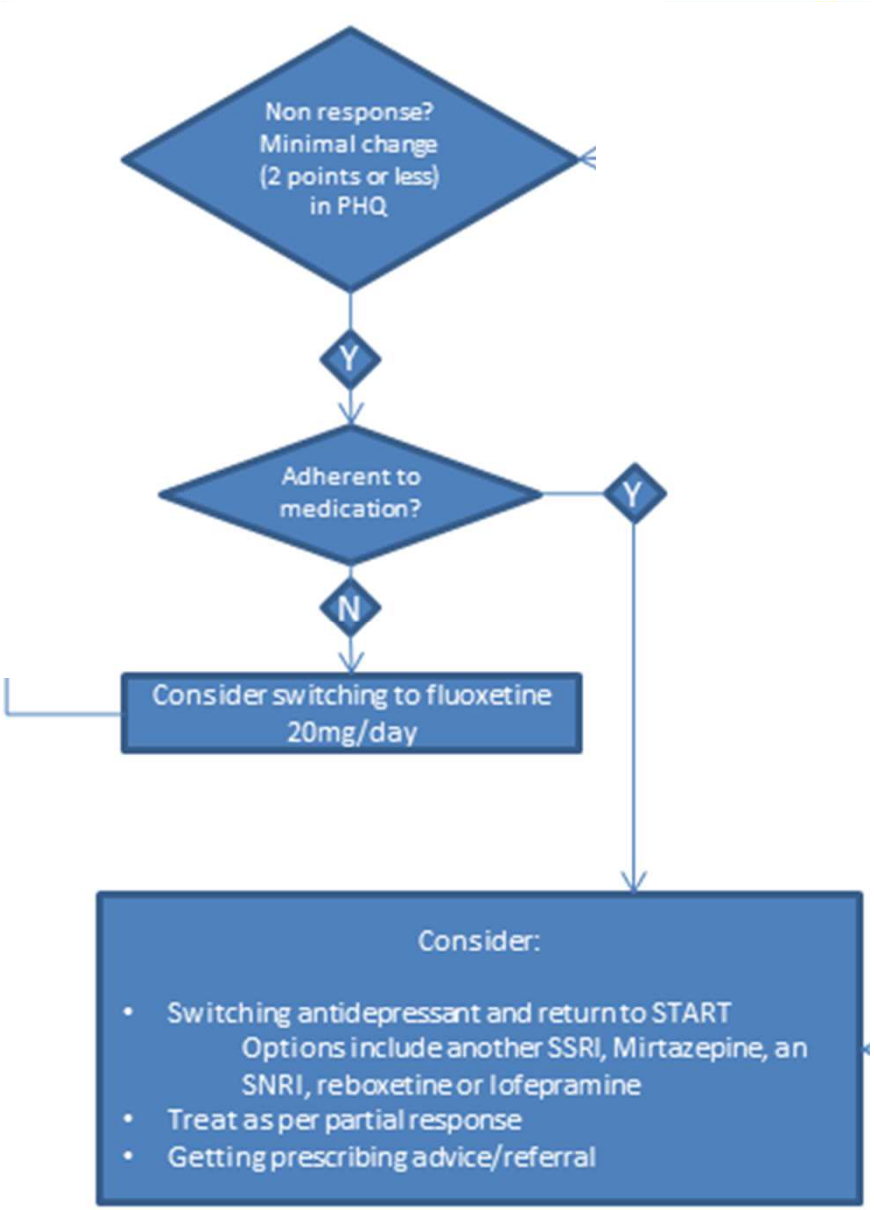
Depression & sleep

- **Don't go straight for a sedative antidepressant in patients with sleep disturbance**
  - The sleep disturbance usually resolves as mood improves
- **However if partial response is due to ongoing sleep disturbance do something about this**
  - CBT for insomnia
  - Hypnotics
  - Increase dose of antidepressant
  - Switch antidepressant (e.g. mirtazepine)

Rule of thumb!!

Dealing with non-response



Switching antidepressant vs increasing dose of current one

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- **If partial response and tolerability try increasing the dose**
  - Probably only do this once with SSRIs
- **If absolutely no response (esp. after one increase in dose)**
  - Switch drug

Rule of thumb!!

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How to switch antidepressants

Rule of thumb!!

- **Abruptly from one to the other**
- **Exceptions**
  - if on high doses reduce for a week (or 4-5 weeks in the case of fluoxetine) before making the abrupt switch
  - SSRI to a TCA: Taper and stop the SSRI and wait 4-7 days (or 4-5 weeks if switching from fluoxetine) and then introduce the TCA.
  - MAOIs – take care!

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Beyond switching/increasing

- Lithium augmentation
  - Mainly done with SSRIs, SNRIs, TCAs and MAOIs
  - Aim for level of 0.6-0.8 mmol/l
- Antipsychotic augmentation
  - Quetiapine licensed; aripiprazole supported by data but not licensed; others less data
- Antidepressant combinations
  - Mixed evidence
  - Mostly mirtazepine plus SSRI or SNRI
  - Safest and easiest option?
- Others include:
  - T3, l-tryptophan, modafinil, lamotrigine

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Depression: Some key questions

- Who should be treated?
- Treatment: what and how?
  - A comment on comorbidity
- ……and then what?

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Pain and anxiety in depression

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- Is very common
  - More than 50% of patients with depression will also meet criteria for a full blown anxiety disorder
  - Patients with depression are 3X more like to be suffering pain as the general population
- Patients with depression plus pain or anxiety respond less well to medication

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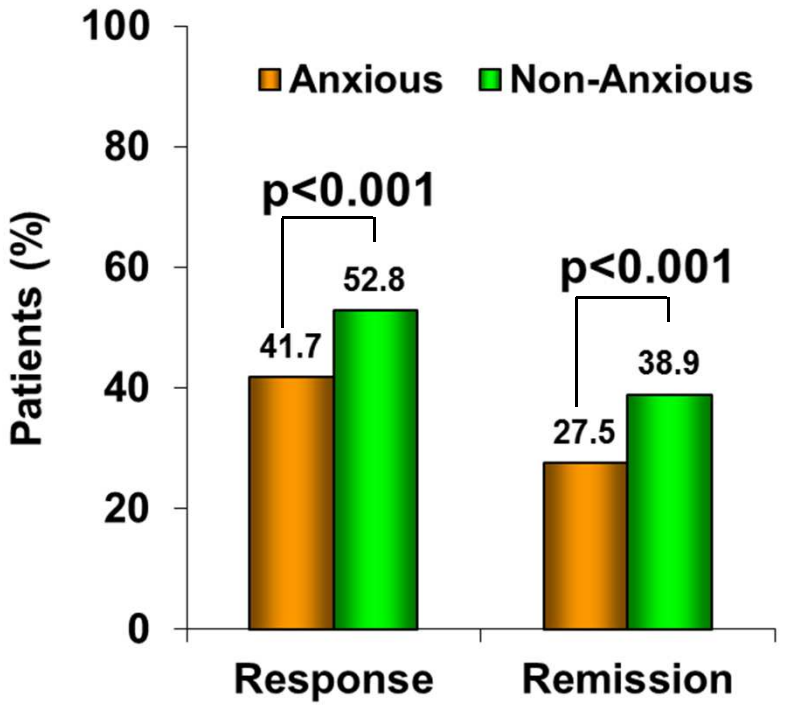
Comorbid anxiety leads to worse outcomes

- STAR*D study N=2,876
- Patients with MDD
- Treated with citalopram for 12 weeks
- Anxious patients defined as:
  - ≥ 7 on anxiety/somatisation
- Response and remission rated with HAMD and QIDS-SR



Fava M, et al. *Am J Psychiatry* 2008;165:342–51.

Baseline pain severity influences response to treatment

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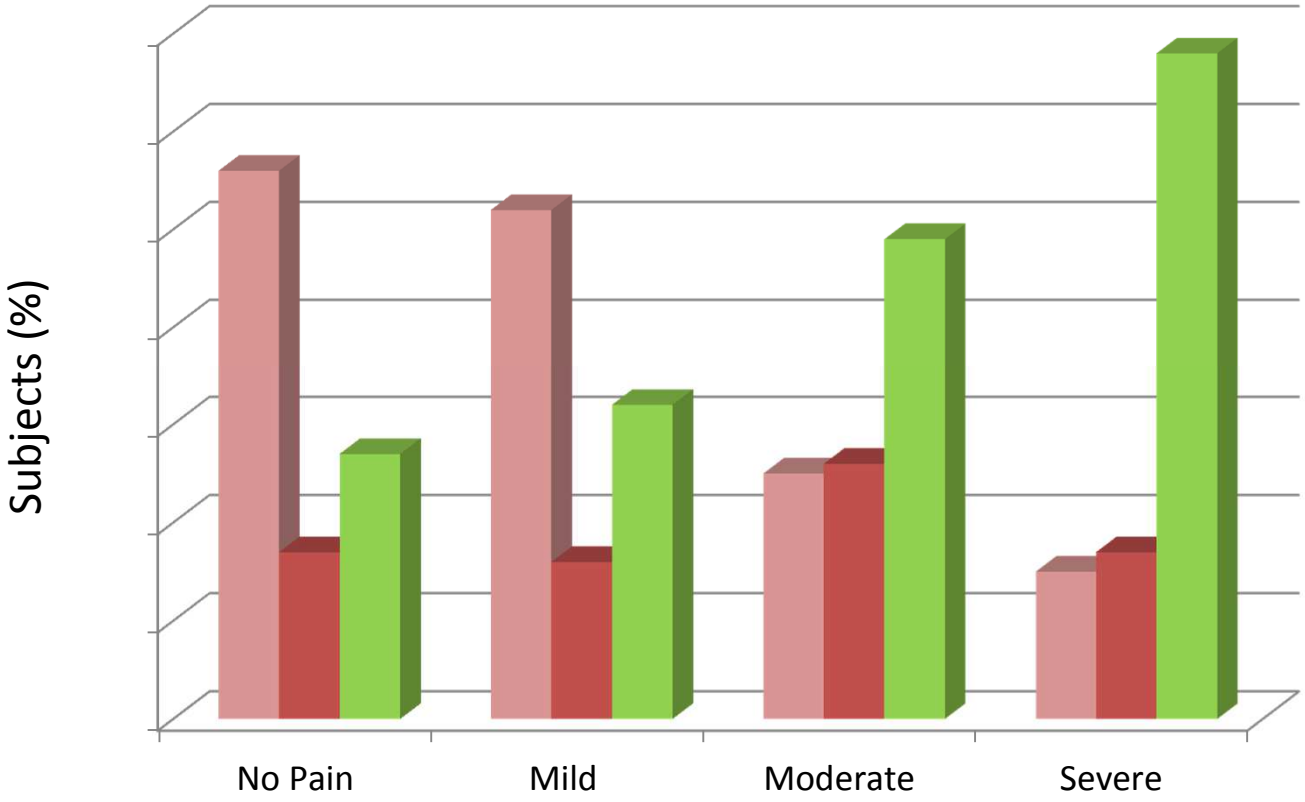
Depression response at 6 months by baseline pain severity



Pain measured with PHQ-15 Depression severity measured with symptom checklist -20

ARTIST – 9 month randomised open-label effectiveness trial (n=573 primary care depressed patients) comparing 3 SSRIs on HRQoL and physical symptoms.

DeVeaugh-Geiss AM, et al. *Pain Medicine* 2010;11:732–41.

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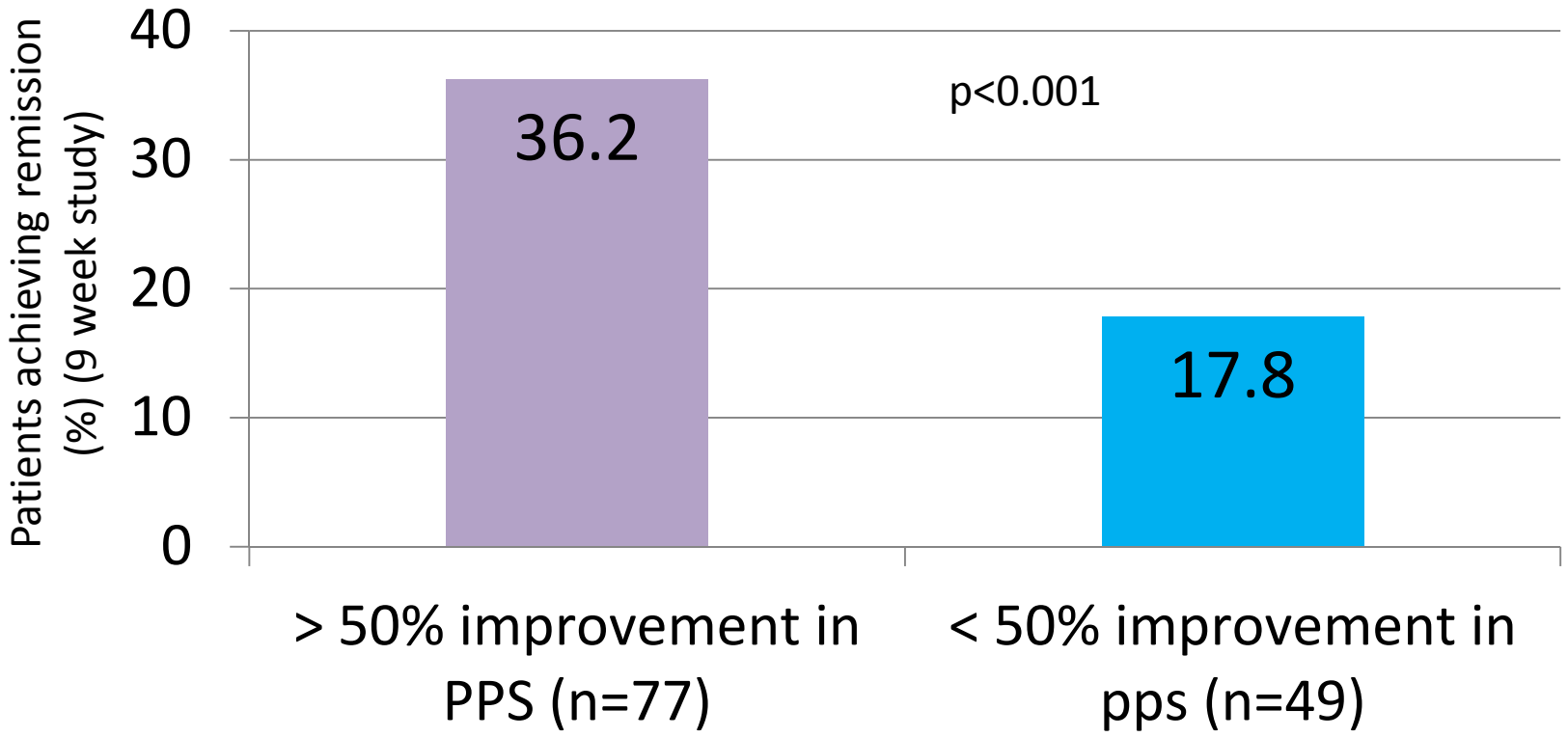
Improvement in painful physical symptoms is associated with increased remission rate



Remission was defined as a HAM-D_{17} Total Score ≤7
Painful physical symptom (PPS) improvement was measured by the Visual Analogue Scale for overall pain

Fava M, et al. *J Clin Psychiatry*. 2004;65(4):521–30.

Pain and anxiety in depression

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- Is very common
  - More than 50% of patients with depression will also meet criteria for a full blown anxiety disorder
  - Patients with depression are 3X more like to be suffering pain as the general population
- Patients with depression plus pain or anxiety respond less well to medication
- Comorbid pain and anxiety can lead to inappropriate treatment
  - Over-sedation of anxious patients
  - Dangerous combinations of antidepressants in those with pain

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Depression and pain

- Drugs do not follow sign posts to different symptoms!

Rule of thumb!!

- **AVOID a patient ending up on amitriptyline for pain (or anything else) PLUS an SSRI**
  - SSRIs can inhibit the metabolism of tricyclics leading to toxic plasma concentrations
  - Use amitriptyline at a full antidepressant dose (e.g. 150mg) or switch both to venlafaxine or duloxetine

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Depression: Some key questions

- Who should be treated?
- Treatment: who, what and how?
- ……and then what?

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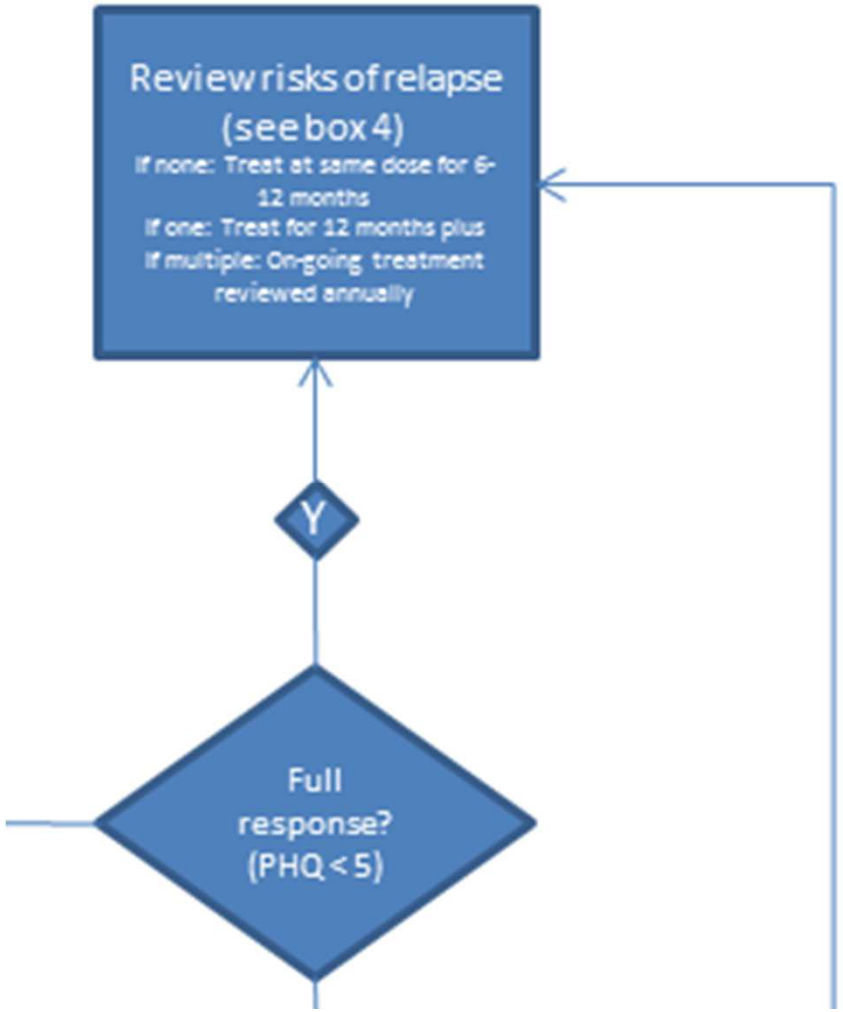
Once in full remission……



- Presence of residual symptoms – increases the risk significantly
- Number of previous episodes – high risk if 2-3 + previous episodes
- Severity and duration – increased risk if severe or lasting more than 6 months
- Degree of treatment resistance of the most recent episode

NB – use clinical judgement

Maintenance

- **Treat for 6-12 months from remission**
  - if any risk factors then longer
  - If multiple risk factors then review annually
  - **Residual symptoms is the biggest risk factor**

Rule of thumb!!

Stopping treatment

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- Be aware of symptoms of discontinuation and warn patients
  - sleep disturbance, GI symptoms, lethargy, headache, affective symptoms, paraesthesiae
- Take into account the clinical situation to determine the rate of taper
  - Serious adverse events may warrant rapid discontinuation
  - Otherwise minimum 4 weeks taper
  - Taper of some months for planned withdrawal after long-term prophylaxis
- If a discontinuation reaction does occur:
  - explanation and reassurance
  - if not sufficient restart antidepressant and tapered more slowly

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Conclusions

- The management of depression is complex
  - Careful diagnosis is required
    - beware misdiagnosed bipolar disorder
    - Assess duration and severity since this influences treatment
  - Treat early and preferably follow an algorithm
  - Partial remission is not good enough
  - Comorbidities can lead to miss-treatment
    - Avoid over sedating anxious patients
    - Avoid combining an SSRI and a tricyclic
  - Once in remission treat for minimum of 6-12 months
  - For patients who are treatment refractory to a couple of antidepressants, lithium, quetiapine or aripiprazole augmentation or mirtazepine + SSRI or SNRI are options