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The problem of partial remission in MDD

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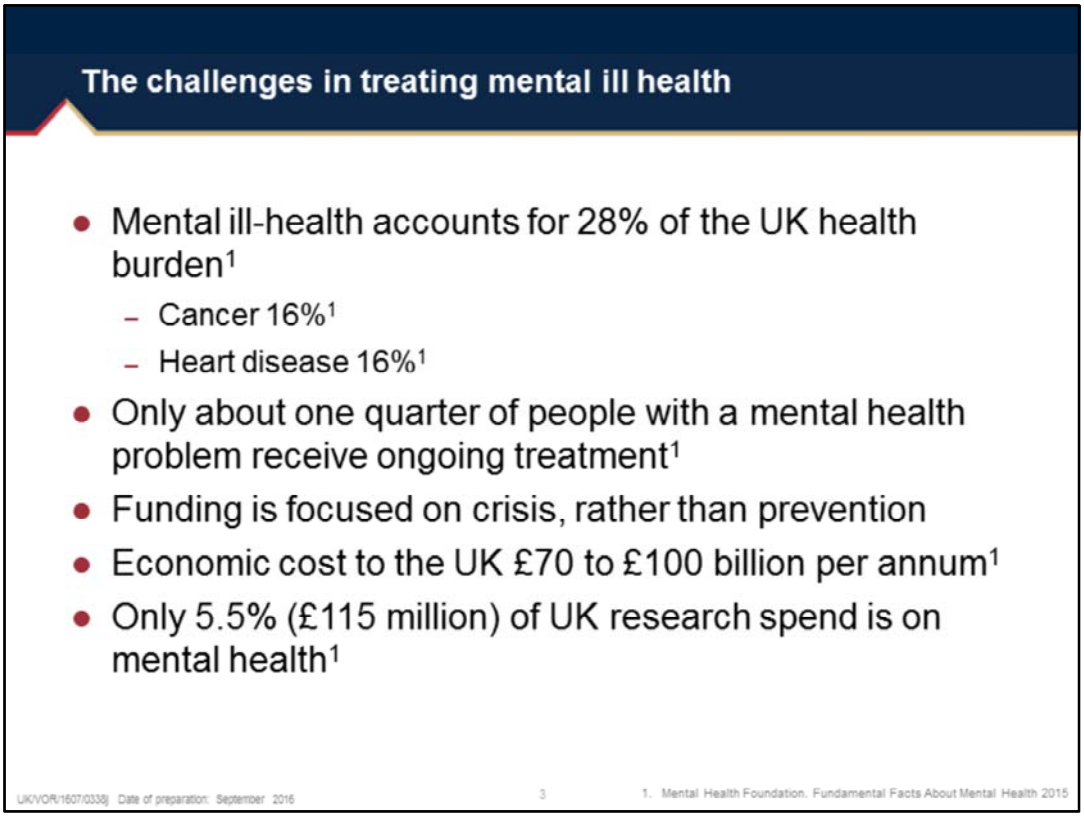
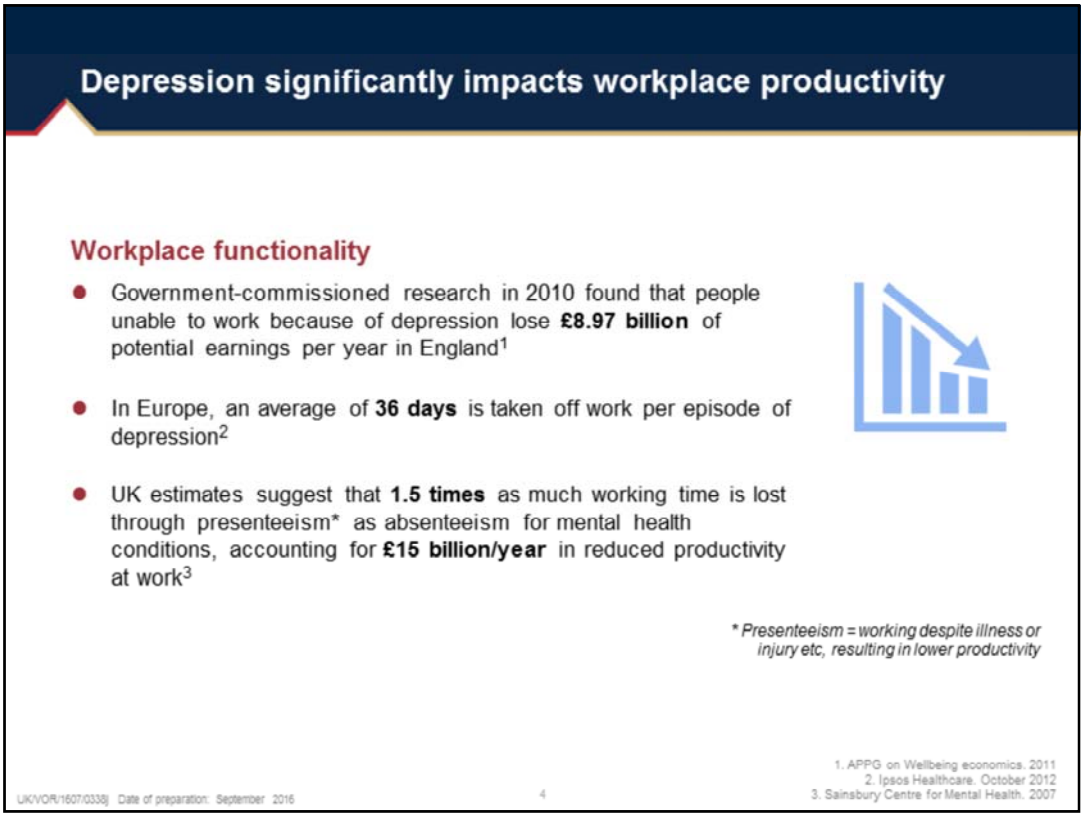
Declaration of Interests



Reference:
1. Mental Health Foundation. Fundamental Facts about Mental Health 2015. October 2015. Accessed at: https://www.mentalhealth.org.uk/sites/default/files/fundamental-facts-15.pdf



Key point: Cognitive dysfunction of depression negatively impacts workplace functionality.

- Government-commissioned research in 2010 found that people unable to work because of depression lose £8.97 billion of potential earnings per year in England.[1]
- In Europe, an average of **36 days** is taken off work per episode of depression[2]
- UK estimates suggest that **1.5 times** as much working time is lost through presenteeism* as absenteeism for mental health conditions, accounting for **£15 billion/year** in reduced productivity at work[3]
- In MDD, cognitive impairments in information processing, memory, and verbal fluency may impact upon academic, occupational, and daily functioning.[4]
- In the United States, the costs related to both absenteeism from work and lost productivity during work due to untreated depression are over **$51 billion** per year.[5]

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1. All-Party Parliamentary Group on Wellbeing Economics: Cost of depression in England 2010, published 2011. Accessed at https://wellbeingeconomics.files.wordpress.com/2012/02/costofdepressionstats2010.pdf
2. IDEA: Impact of Depression at Work in Europe Audit Final report. *Ipsos Healthcare*. October 2012
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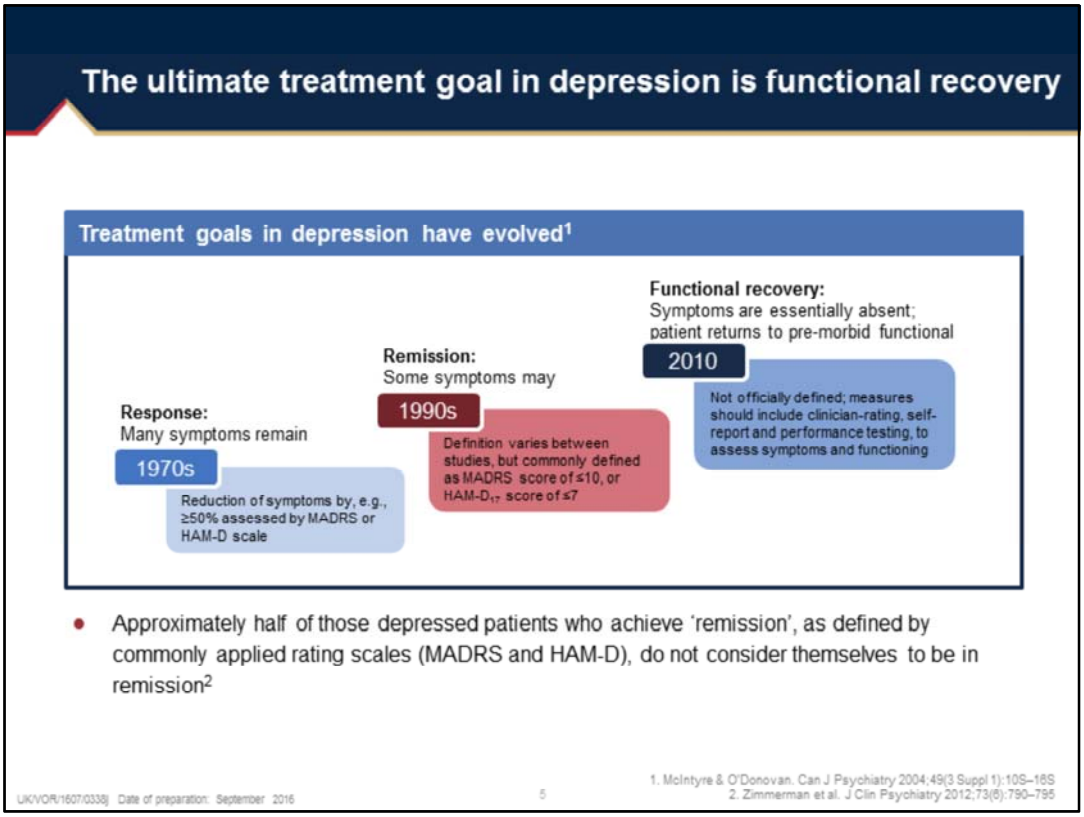
4. Hammar A, Ardal G. Cognitive functioning in major depression – a summary. *Frontiers in Human Neuroscience* 2009; 3: 26
5. Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey-Lisle PK. The economic burden of depression in the united states: How did it change between 1990 and 2000? *The Journal of Clinical Psychiatry* 2003; 64(12): 1465–1475



Key point: The ultimate goal of treatment in depression is functional recovery.

The goals of depression therapy have evolved over time, from response, to remission, with functional recovery now being seen as the ultimate goal of treatment.[3]

Response and remission
In research settings, the term 'response' usually denotes a 50% reduction (improvement) in depression scores, while the term 'remission' refers to the elimination of most active depressive symptoms (for example, a 17-item Hamilton Rating Scale for Depression [HAM-D_{17}] score ≤7, or a Montgomery-Åsberg Depression Rating Scale [MADRS] score ≤10).[1,3] However, approximately half of depressed patients in remission based on a HAM-D_{17} score ≤7 do not consider themselves to be in remission, which raises questions about the validity of the HAM-D and other symptom-based definitions of remission to guide treatment decision-making in clinical practice.[2] Remission measures, such as these, are rarely used in clinical practice, however. In the DSM-5, remission is defined as >2 months of no significant symptoms of depression.[4]

Functioning
In addition to depressive symptomatology, patients and physicians agree that functioning is important in defining a 'cure'.[3,5] Beyond the clinician rating, the patient perception of treatment success is important.[1] The Sheehan Disability Scale (SDS) is a short, patient-assessed measure of functioning in areas of work, social, and family life.[6]

While there are no officially-defined treatment goals in depression, contemporary treatment should be focused on achieving full recovery, with the patient returning to their pre-morbid functional status, with no residual symptoms.

References

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4. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, APA 2013.
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Model of depression and treatment

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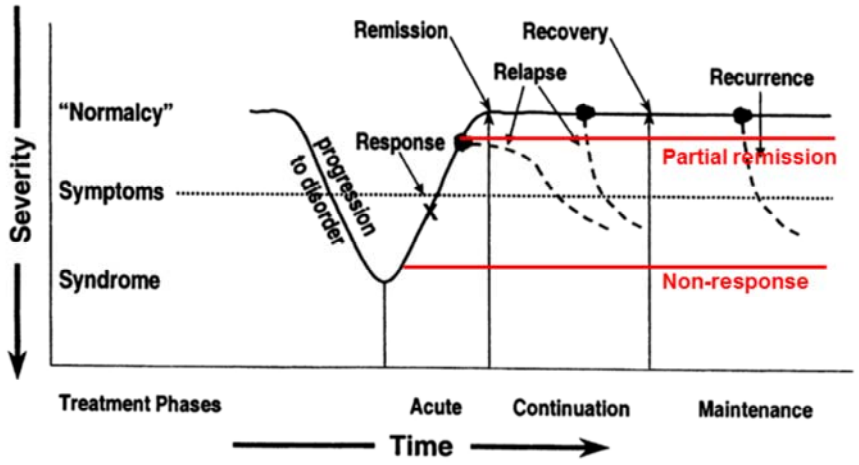
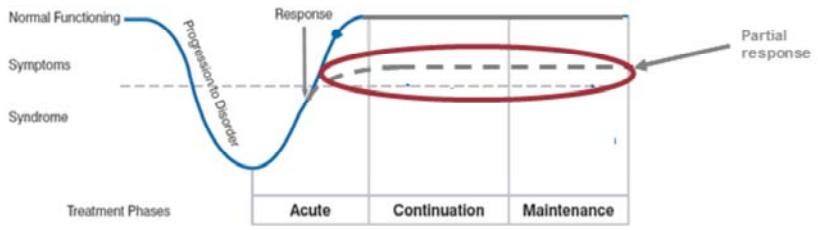


Frank et al 1991

What about the patients that don't reach functional recovery?



Adapted from Kupfer, 1991 [1]

- **Partial Responders:** Patients who have experienced response following antidepressant therapy but who **still have symptoms of depression** and no longer show any further sign of improvement after an extended period of treatment[2-4]

1. Kupfer DJ. J Clin Psych 1991; 52 (5, suppl): 28–34
2. McClintock SM et al. J Clin Psychopharmacol. 2011; 31(2): 180-186
3. Trivedi MH et al. Am J Psychiatry 2006; 163(1): 28–40
4. Borolato B et al. CNS Neurol Disord Drug Targets 2014; 13: 1804-181

Speaker notes:

- The objectives for the treatment of depressed patients are to:
  - Achieve remission (acute treatment)
  - Prevent relapse (continuation treatment)
  - Prevent recurrence (maintenance treatment)[1]
- A response is defined as a 50% improvement in symptoms as measured by the HAM-D score[5]
- Remission is a virtually symptom-free state – the HAM-D score is ≤ 7[5]
- Relapse is a worsening of symptoms after remission[1]
- Recurrence is the development of a new episode after initial recovery[1]
- The risk of relapse is significantly higher in patients that respond only partially to therapy compared with those who achieve remission (76% versus 25%)[6]

References;

1. Kupfer DJ. Long-term treatment of depression. *J Clin Psych* 1991; 52 (5, suppl): 28–34;
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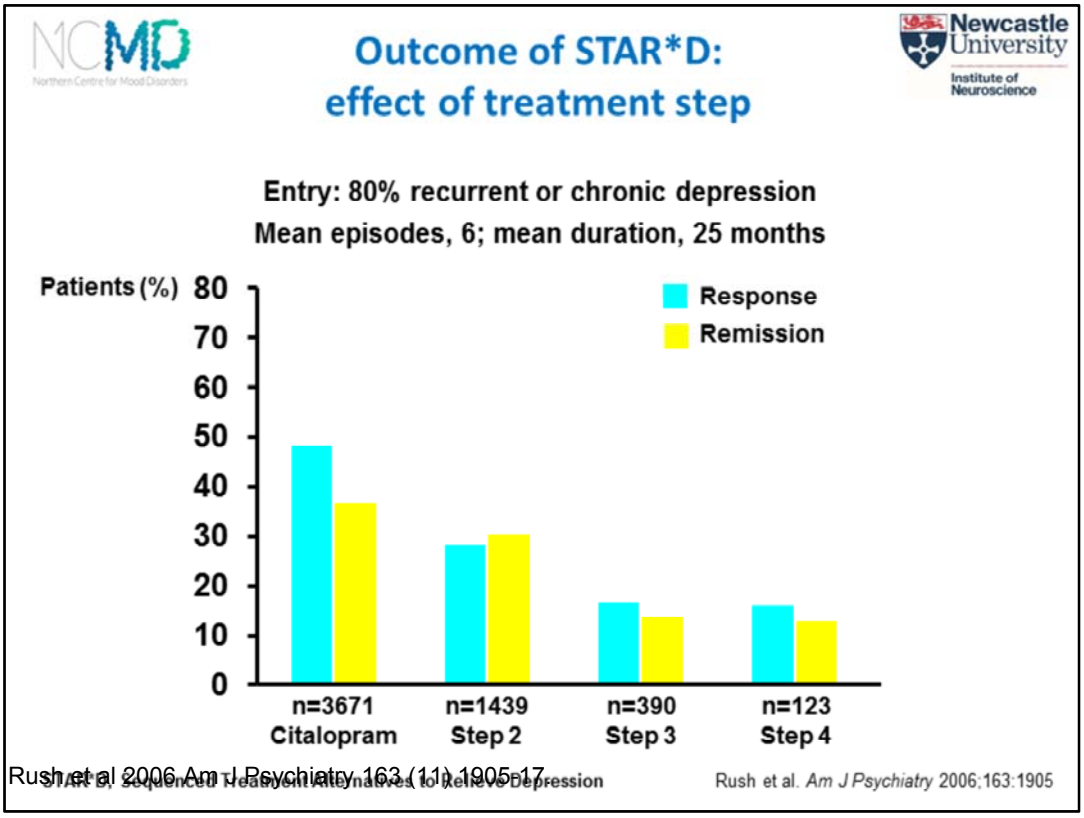
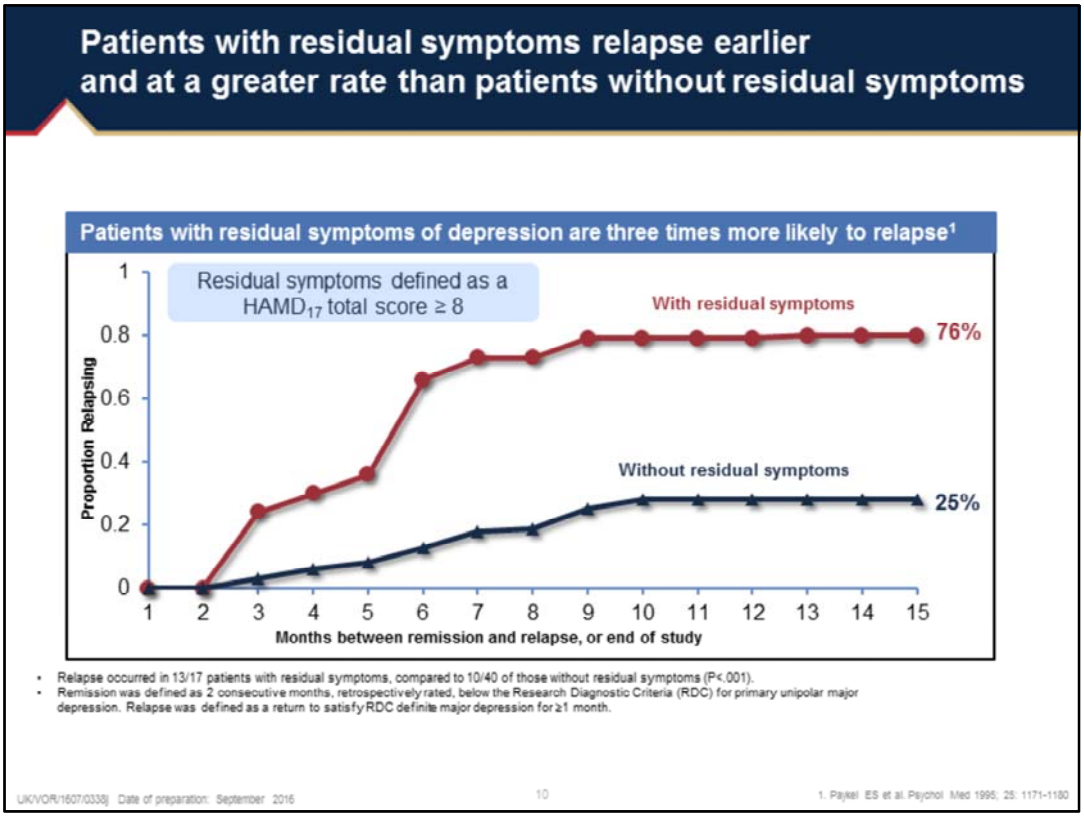


Rush et al 2006 Am J Psychiatry 163 (11) 1905-17

Residual depressive symptoms are associated with:

- Higher risk of relapse
- Shorter time to relapse
- Higher long-term symptom burden
- Increased suicidal behaviour
- Reduced functioning in home life
- Reduced functioning at work



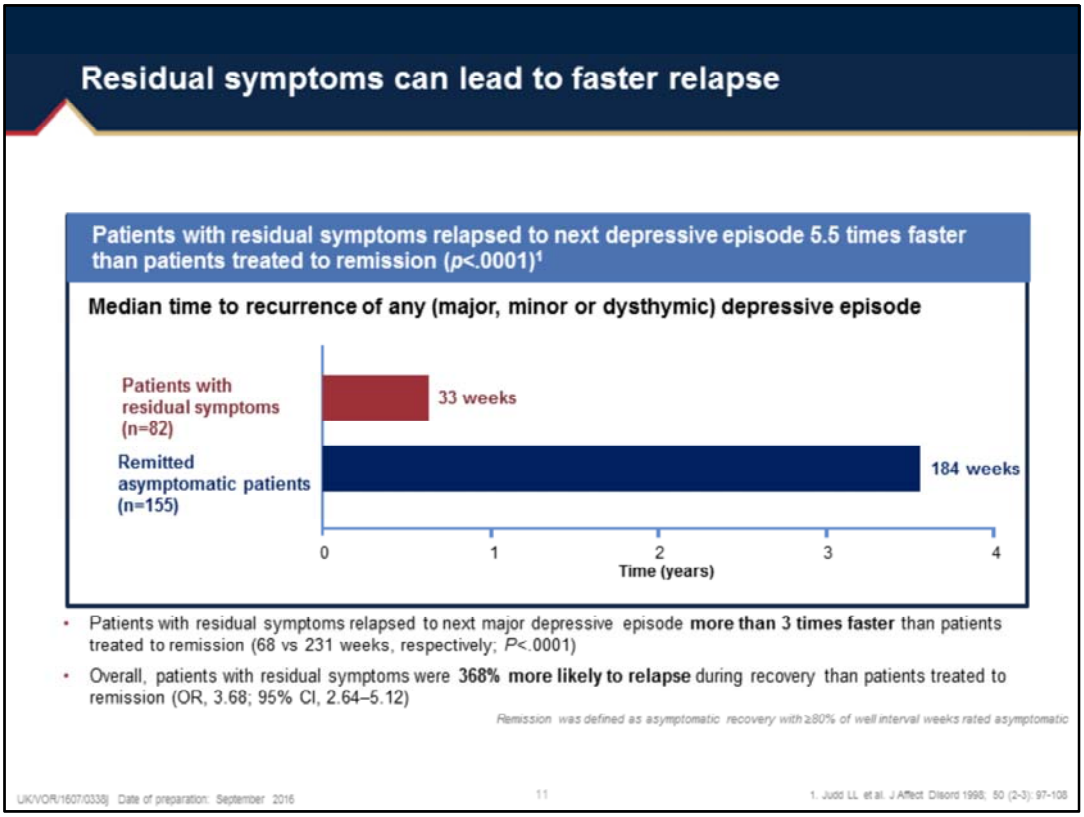
Speaker notes[1]

- KEY POINTS
- These data from Paykel and colleagues reinforce the importance of adequacy of treatment and the point that failure to achieve remission increases the risk of relapse.
- They found that patients with residual symptoms were 3 times more likely to relapse (76% vs 25%).

- BACKGROUND
- Paykel et al systematically followed 60 patients to the point of remission, or until 15 months without remission had elapsed. They specifically examined the outcomes of patients with and without residual symptoms of depression following partial or full remission (defined by improvement in the HAM-D17), and found that residual symptoms were a very strong predictor of subsequent early relapse.
- 19 of the 60 patients (32%) were defined as having residual symptoms (defined as a score of 8 or more on the HAM-D17). The remaining 41 patients reached remission according to the criterion of HAM-D17 < 7. Patients were monitored for 15 months using the Beck Depression Inventory, as well as full psychiatric interviews in order to identify relapse, "defined as a return to Research Diagnostic Criteria definite major depression for at least 1 month, rated retrospectively."
- The relationship between residual symptoms and subsequent relapse was analyzed using the Kaplan-Meier method. They found a marked difference, with a very high relapse rate, in those patients with residual symptoms. Overall, 76% (13/17) of those patients relapsed, as opposed to 25% (10/40) of those who had remitted (did not have residual symptoms). The difference between the 2 survival curves was significant at P<0.001.

Reference

1. Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med* 1995; 25(6): 1171-1180

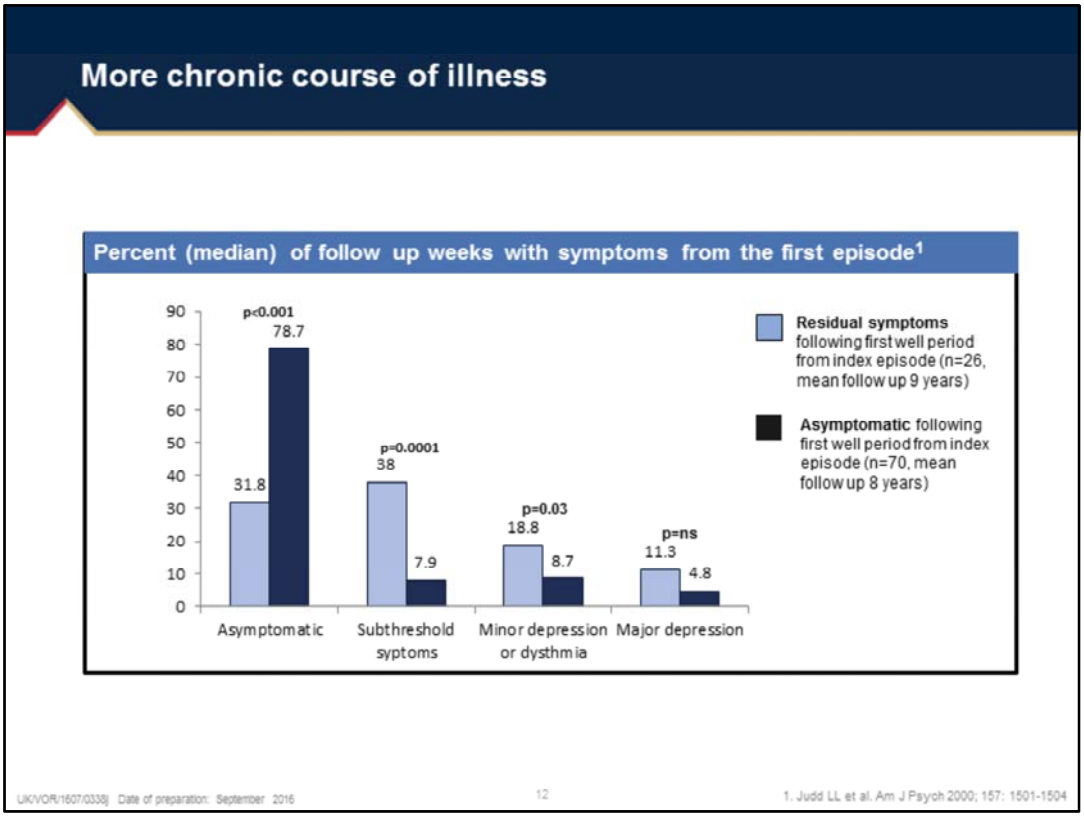


Speaker notes

- A 10-year, NIMH-sponsored study tested whether level of recovery from major depressive episodes (MDEs) predicts duration of recovery in 237 unipolar major depressive disorder (MDD) patients.
- MDD patients seeking treatment at five academic centres were followed naturalistically for 10 years or longer.
- Patients were divided on the basis of intake MDE recovery into residual mild depressive symptoms (SSD; n=82) and asymptomatic (n=155) recovery groups.
- They were compared on time to first episode relapse/recurrence, antidepressant medication, and comorbid mental disorders. Recovery level was also compared to prior history of recurrent MDEs (>4 lifetime episodes) as a predictor of relapse/recurrence.
- Residual SSD compared to asymptomatic recovery patients relapsed to their next MDE >3 times faster (median=68 vs 231 weeks) and to any depressive episode >5 times faster (median=33 vs 184 weeks). Residual SSD recovery status was significantly associated with early episode relapse (OR=3.68; 95% CI 2.64-5.12 vs asymptomatic) and was a stronger predictor of relapse than history of recurrent MDEs (OR=1.64; 95% CI 1.17-2.29; for >4 MDEs vs 1, 2 or 3 prior MDEs) in the asymptomatic group.

Reference

1. Judd LL, Akiskal HS, Maser JD et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. *J Affect Disord*. 1998; 50 (2-3): 97-108



Speaker notes

- This study investigated the influence of incomplete recovery from first lifetime major depressive episodes on long-term outcome.
- After their first lifetime major depressive episode, patients were divided into asymptomatic (n=70) and residual subthreshold depressive symptom (n=26) recovery groups and compared on longitudinal course during up to 12 years of prospective naturalistic follow-up.
- Patients with residual subthreshold depressive symptoms during recovery had significantly more severe and chronic future courses. Those with residual symptoms relapsed to major and minor depressive episodes faster and had more recurrences, shorter well intervals, and fewer symptom-free weeks during follow-up than asymptomatic patients.
- Resolution of major depressive episodes with residual subthreshold depressive symptoms, even the first lifetime episode, appears to be the first step of a more severe, relapsing, and chronic future course. When ongoing subthreshold symptoms continue after major depressive episodes, the illness is still active, and continued treatment is strongly recommended.

Reference

1. Judd LL et al. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am J Psych* 2000; 157: 1501-1504

Journal of Affective Disorders

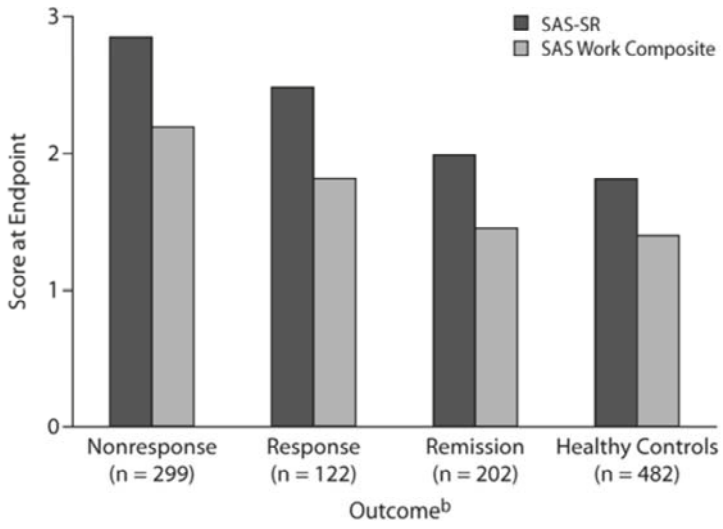
Volume 45, Issues 1–2, 1 August 1997, Pages 5–18

The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder

Lewis L Judd[a], Hagop S Akiskal[a, b], Martin P Paulus[a]

1."Thought of committing suicide" and 2. Attempted suicide significantly increased in SSD.
ORs 4.1 and 3.5 (v MDD 27.3 and 21.8)

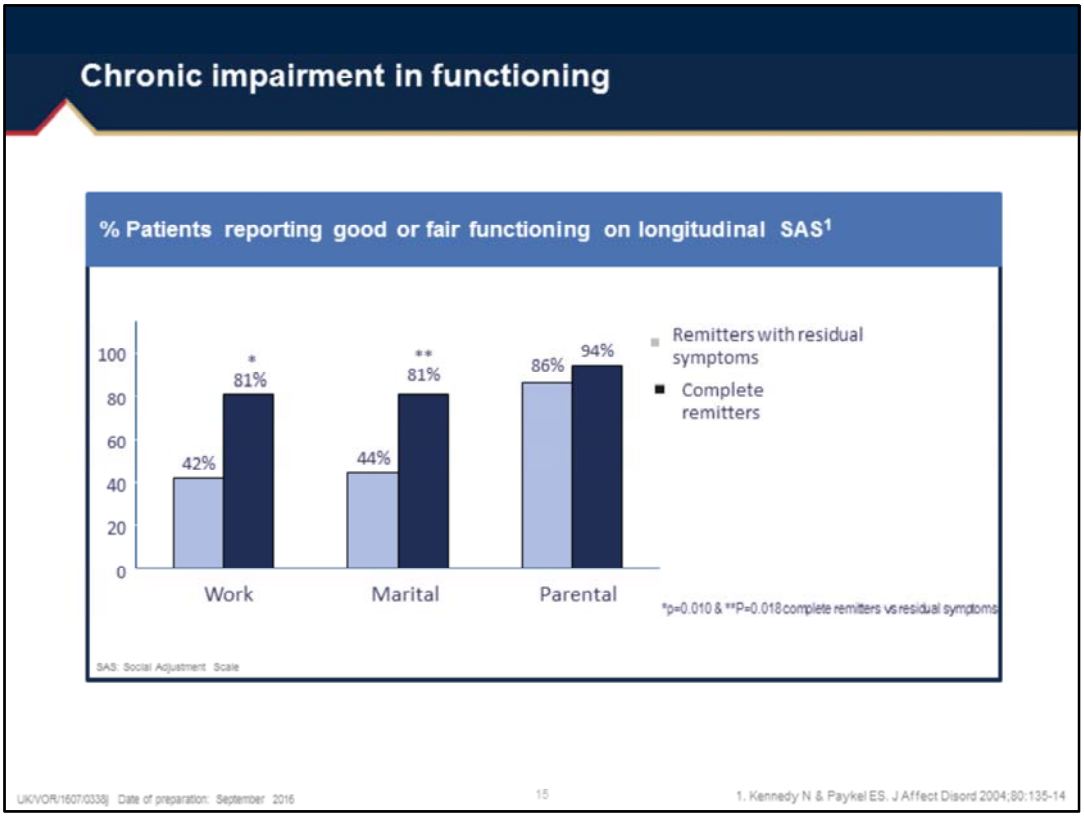
Figure 2. Impairment in Work and Relationships Normalizes Only With Remission[a]



[a]Data from Miller et al.[4]

[b]Significant differences ($P \leq .05$) existed in SAS work composite scores between response vs nonresponse, remission vs nonresponse, and remission vs response.

Abbreviation: SAS–SR = Social Adjustment Scale–Self Report.



Background[1]

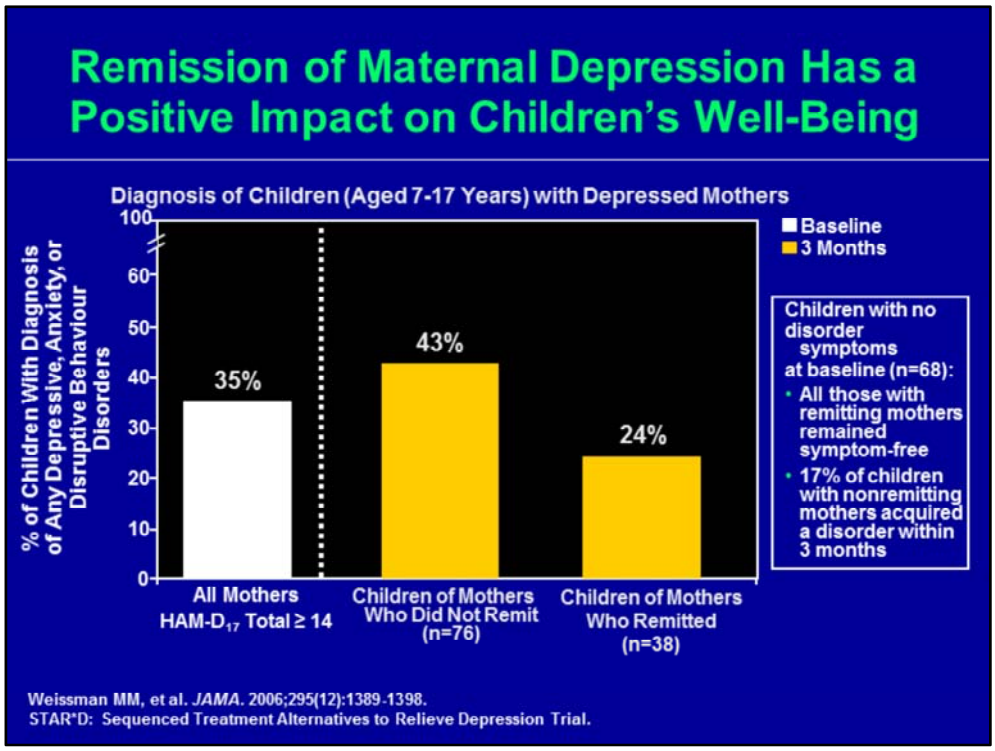
Although residual symptoms after remission from depression are common and predict early relapse, little is known about the impact of residual symptoms on longer-term clinical course of depression or social functioning.

Methods[1]

- Sixty severe recurrent depressives, who remitted from an index episode of depression with residual symptoms or below residual symptomatology, were followed-up at 8–10 years
- Subjects underwent detailed longitudinal interviewing on course of depression, treatment and socioecomonic functioning over follow-up.
- Results: Long-term follow-up data was obtained on all living subjects and 55 (95%) were interviewed. The residual symptoms group spent more time with depressive symptoms over follow-up but not at full criteria for major depression and showed greater impairment in longitudinal and follow-up social adjustment.
- No significant differences were found between the two groups in percentage recurring long-term, mean number of recurrences, readmissions, chronic episodes or clinical global outcome criteria.
- Limitations: Long-term clinical and social outcomes were assessed by a single retrospective longitudinal interview. Conclusions:
- **Patients who remit from depression with residual symptomatology continue to have more depressive symptoms and impaired social functioning long-term and may need more aggressive treatment**

References

1. Kennedy N & Paykel ES. Residual symptoms at remission from depression: impact on long-term outcome. *J Affect Disord* 2004;80:135-14



PURPOSE OF THE SLIDE
- Provide information about the impact of depression on the well-being of children (7-17 years old) who had mothers who were depressed.

SPEAKER DIRECTION
- Achieving remission can be extremely important to families.
- In this data from the STAR*D-Child Report, remission of maternal depression had a positive impact on children's well-being and non-remission had a negative impact over a 3-month acute treatment period.
- The children (7-17 years old) were assessed at baseline and endpoint for any depressive, anxiety, or disruptive behavior disorders.
- Overall, there was an 11% decrease in rates of diagnosis for children (n=38) whose mothers remitted vs an 8% increase shown for children whose mothers did not remit after 3 months of treatment (p=.01). Lack of statistical power prevents ascertainment of significance of changes for individual diagnosis.
- Among children with no disorder symptoms at baseline (n=68), those with remitting mothers remained symptom-free while 17% of children of non-remitting mothers acquired a disorder over the 3-month study period.

BACKGROUND
- Maternal depression = HAM-D_{17} Total ≥14 at baseline
- Maternal remission = HAM-D_{17} Total ≤7
- The STAR*D-Child Report, an ancillary study to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) multi-center trial, was conducted to determine if any benefit is conferred to the children of a mother who is depressed and achieves remission.
- The assessment tool for children was the Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version sections that target affective, anxiety, and disruptive behavior.
- Children whose mothers' depression had remitted showed a decrease in the rates of depressive (18% vs 9%) and disruptive behavior disorders (18% vs 12%) but with no change in anxiety disorders. Children whose mothers did not remit showed an increase in the rates of depressive (7% to 11%), anxiety (17% to 25%), and disruptive behavior (20% to 24%) disorders.

REFERENCE
Weissman MM, Pilowsky DJ, Wickramaratne PJ, et al. Remissions in maternal depression and child psychopathology, a STAR*D-Child Report. *JAMA.* 2006;295(12):1389-1398.

The patient returned to the GP with residual symptoms

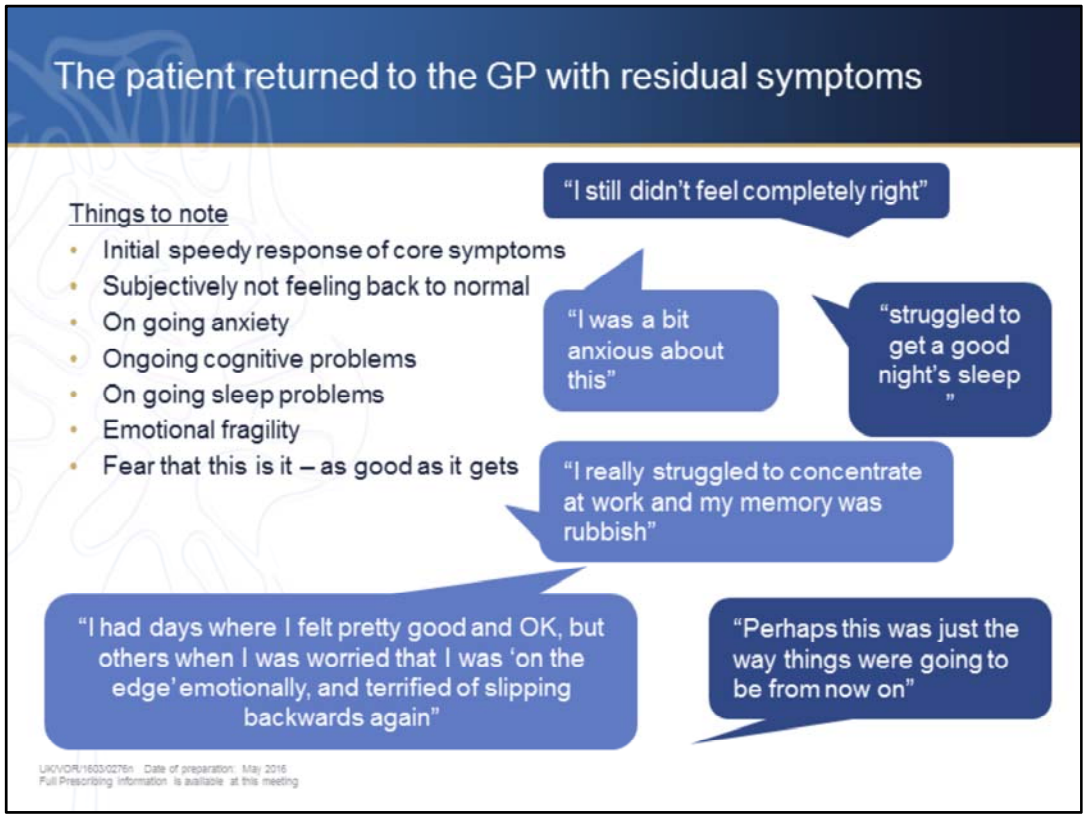
Things to note

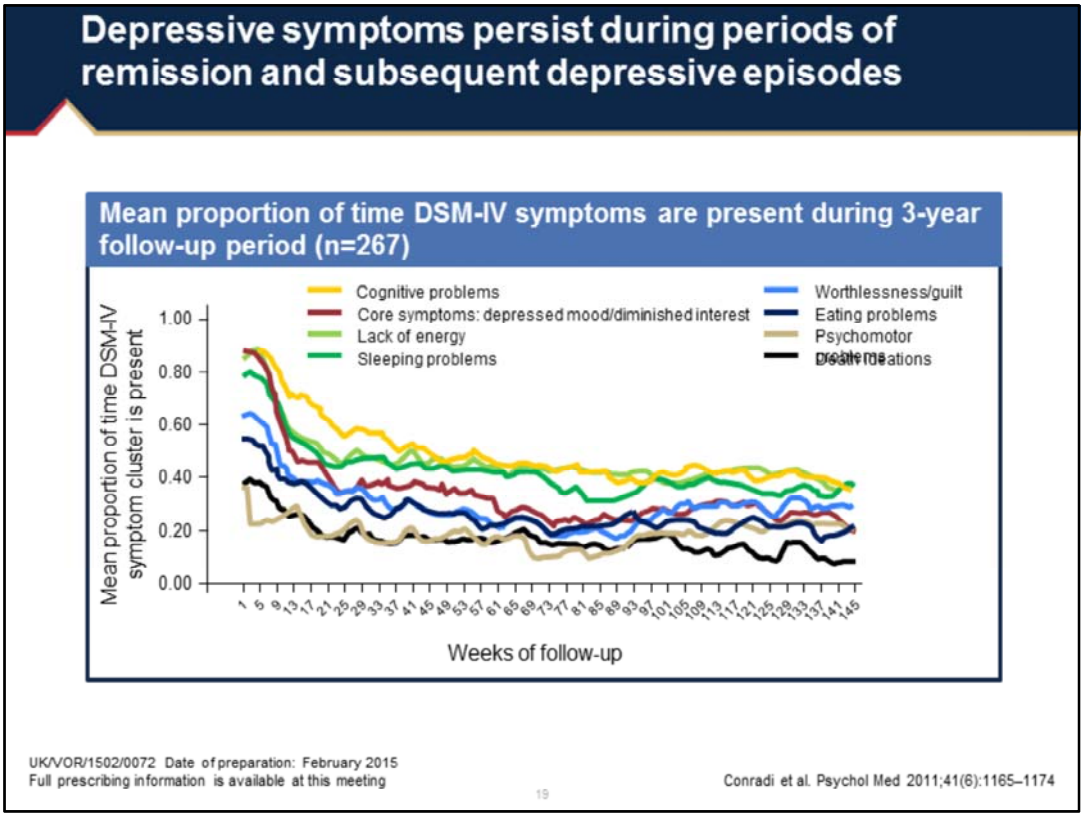
- **Initial speedy response of core sympto**
- Subjectively not feeling back to normal
- On going anxiety
- Ongoing cognitive problems
- On going sleep problems
- Emotional fragile
- Fear that this is it – as good as it gets

"When I started taking the antidepressant, at first it was remarkable how well it worked. Although the doctor said it would take some time for them to work, within a week I was feeling brighter in myself and my sleep improved"

"After another couple of weeks, I started to get my interest in things back"

UK/VOR/1603/0276n Date of preparation: May 2016
Full Prescribing Information is available at this meeting


The patient returned to the GP with residual symptoms
Things to note
Initial speedy response of core symptoms
Subjectively not feeling back to normal
On going anxiety
Ongoing cognitive problems
On going sleep problems
Emotional fragility
Fear that this is it – as good as it gets
"I still didn't feel completely right"
"I was a bit anxious about this"
"struggled to get a good night's sleep"
"I really struggled to concentrate at work and my memory was rubbish"
"I had days where I felt pretty good and OK, but others when I was worried that I was 'on the edge' emotionally, and terrified of slipping backwards again"
"Perhaps this was just the way things were going to be from now on"
UK/VOR/1603/0276n Date of preparation: May 2016
Full Prescribing Information is available at this meeting



Key point: In depression, rates of overall residual symptomatology are high.[1] Symptoms with high residual rates, such as cognitive problems, need continuous attention to prevent relapse.[1]

Residual depressive symptomatology constitutes a substantial risk for relapse in depression.[2] Treatment until full remission is achieved is therefore needed.[3]

The presence of residual symptoms was studied in a 3-year follow-up of 267 initially depressed primary care patients.[1] Patients received one of four treatment interventions:[1]

- usual care by the GP (brief supportive counselling, possible antidepressant treatment, and/or referral according to clinical guidelines)
- psycho-educational prevention programme (low-intensity programme consisting of three face-to-face sessions, and short 3-monthly telephone contacts thereafter)
- psycho-educational prevention programme plus psychiatric consultation
- psycho-educational prevention programme brief cognitive behavioural therapy.

The severity of the index depressive episode was moderate or severe in 70% of patients, and 74% of patients were receiving antidepressant medication at baseline.[1]

The presence of individual DSM-IV depressive symptoms during subsequent depressive episodes and periods of partial remission were assessed by patient interviews at 3-monthly intervals to establish the presence/absence of individual DSM-IV criteria or symptom clusters per week during the past 3 months.[1]

The slide illustrates the course of individual depressive symptoms during the 3-year follow-up.[1] At study entry, nearly all of the patients were suffering from a major depressive episode – reflected in the high prevalence of most of the symptoms at baseline.[1] During the entire 3-year follow-up, cognitive problems, lack of energy, sleeping problems, and depressed mood/diminished interest were present 58–66% of the time.[1] During non-major depressive episodes, 21% of patients

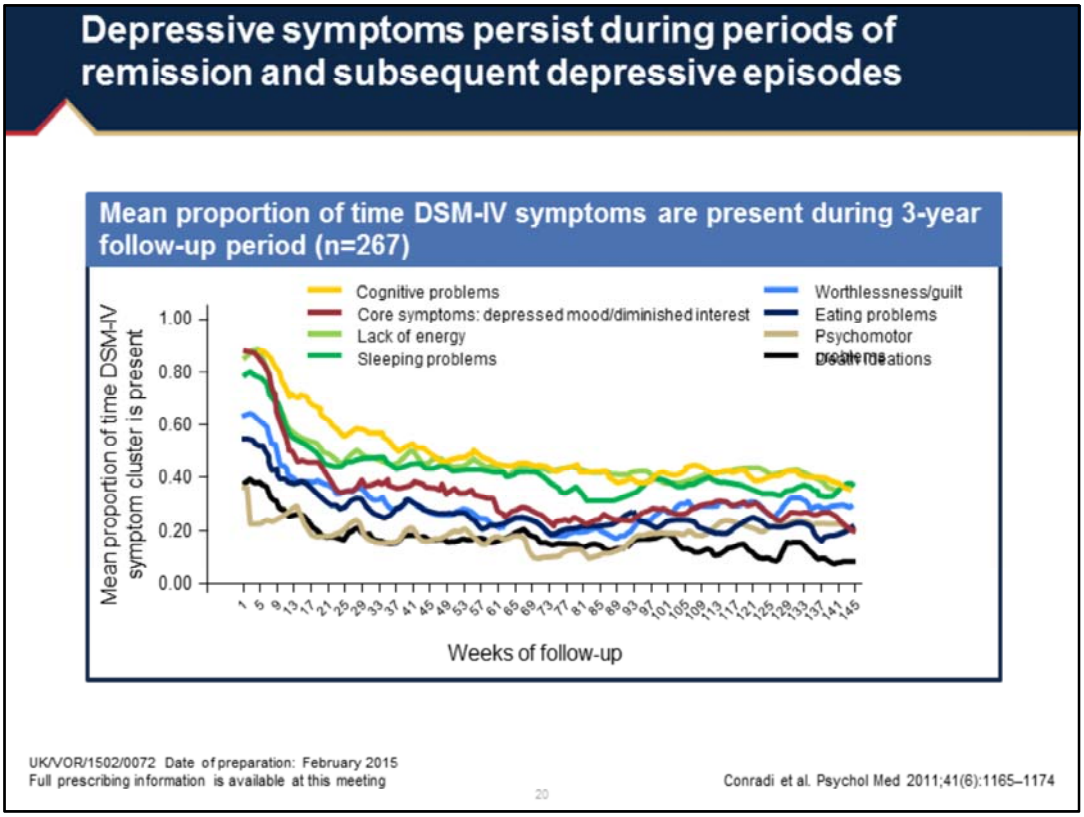
reported depressed mood/diminished interest, while 44% of patients reported cognitive problems, 39% reported sleeping problems, and 35% reported lack of energy.[1] Thoughts of death were reported by 11% of patients.[1]

Rates of overall residual symptomatology were fairly high.[1] At any point during non-major depressive episodes, criteria for two DSM-IV depressive symptom clusters were met.[1] Thus, as measured by presence of residual symptoms, depression is indeed a chronic disease.[1]

Partial remission is very common and constitutes a challenge for clinical practice.[1] Symptoms with high residual rates need continuous attention to prevent relapse.[1] However, physicians also need to be alert to the less prevalent residual symptoms, such as thoughts of death, as these symptoms may constitute a higher risk of relapse.[1]

References

1. Conradi HJ, et al. Psychol Med 2011; 41 (6): 1165–1174.
2. Judd LL, et al. J Affect Disord 1998; 50 (2–3): 97–108.
3. American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. Third edition. Arlington, VA, 2010.



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References

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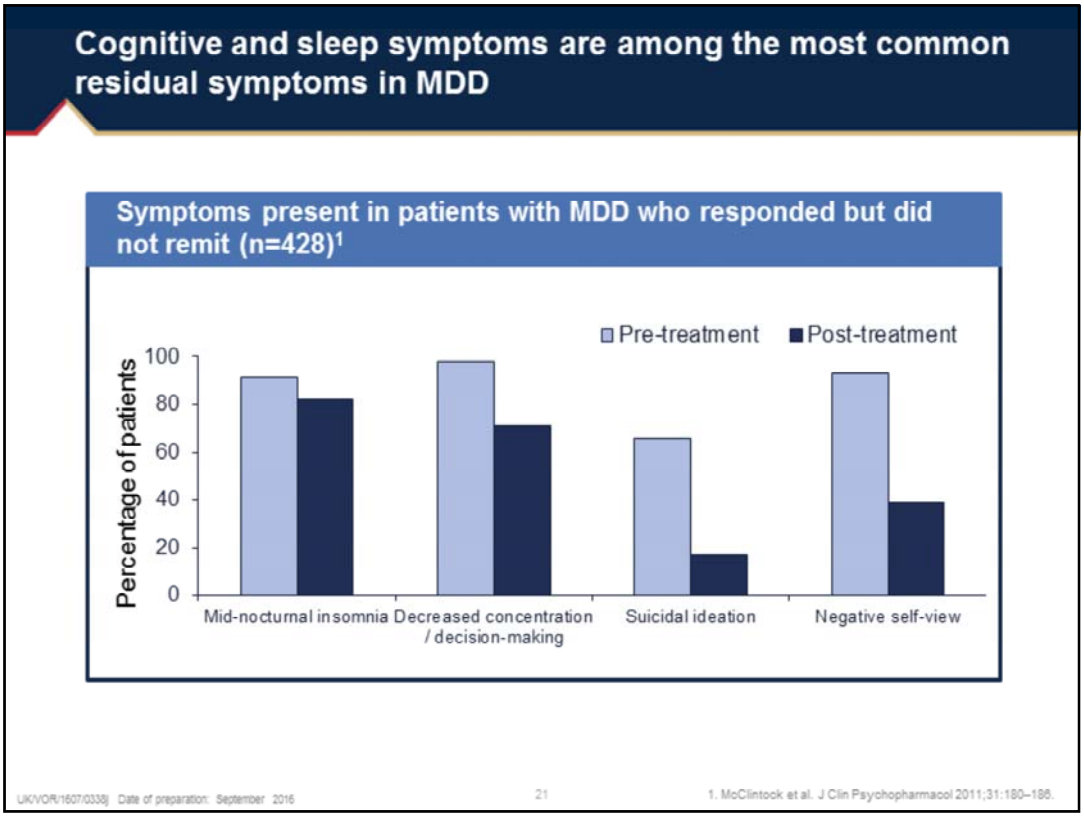
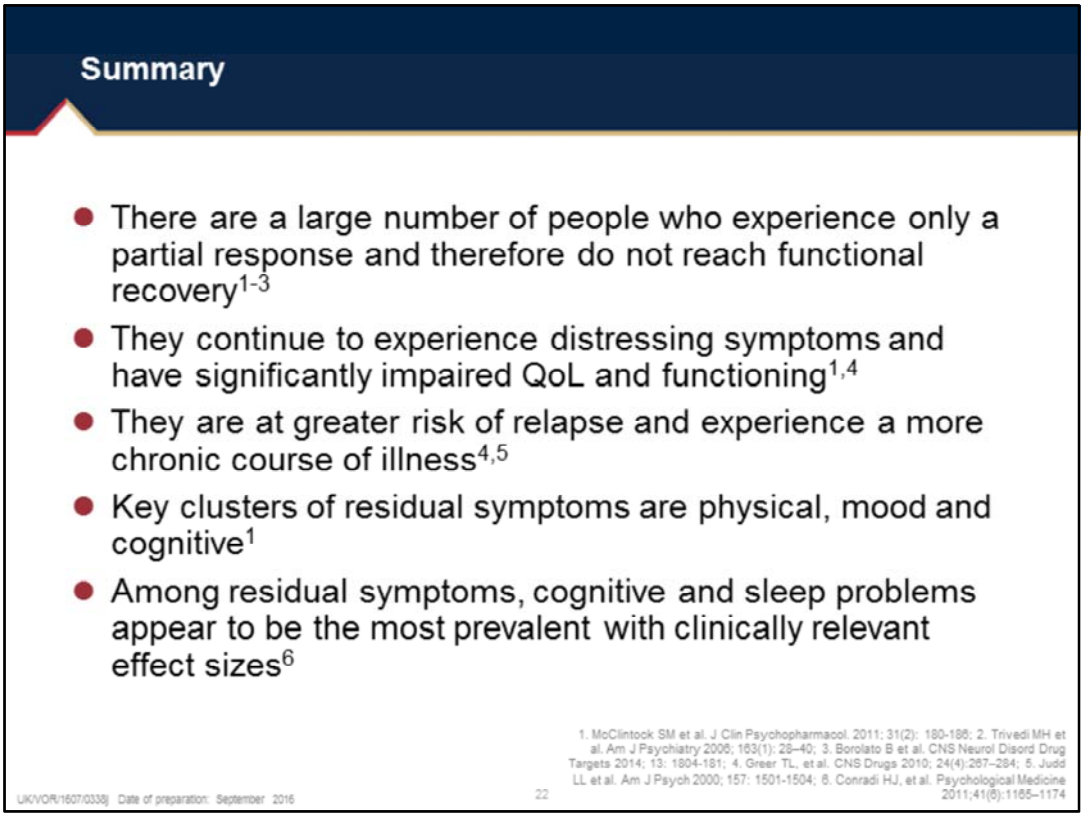


Key point: In the STAR*D trial, cognitive symptoms were among the most common residual symptoms experienced by patients who responded to treatment.

- Mid-nocturnal insomnia, decreased concentration/decision-making, suicidal ideation and negative self-view were all common residual symptoms.[1]

Reference

1. McClintock SM, et al. Residual symptoms in depressed outpatients who respond by 50% but do not remit to antidepressant medication. *Journal of Clinical Psychopharmacology* 2011;31:180–186.



References

1. McClintock SM et al. Residual symptoms in depressed outpatients who respond by 50% but do not remit to antidepressant medication. *J Clin Psychopharmacol*. 2011; 31(2): 180-186
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Why do some patients not achieve full functional recovery with treatment?

- Wrong diagnosis
  - e.g. bipolar rather than unipolar
- Diagnostic comorbidities
  - Pain, anxiety, substance misuse, personality disorder
- Biology of the disorder
  - "Depression" is probably not a pathophysiologically homogeneous disorder
- Wrong (or not ideal) treatment for that patient
- Patient not adherent to treatment
- Treatment trials are inadequate
- Psychosocial maintaining factors

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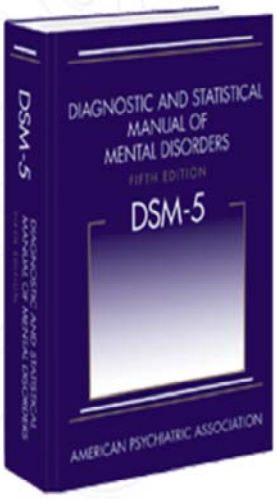
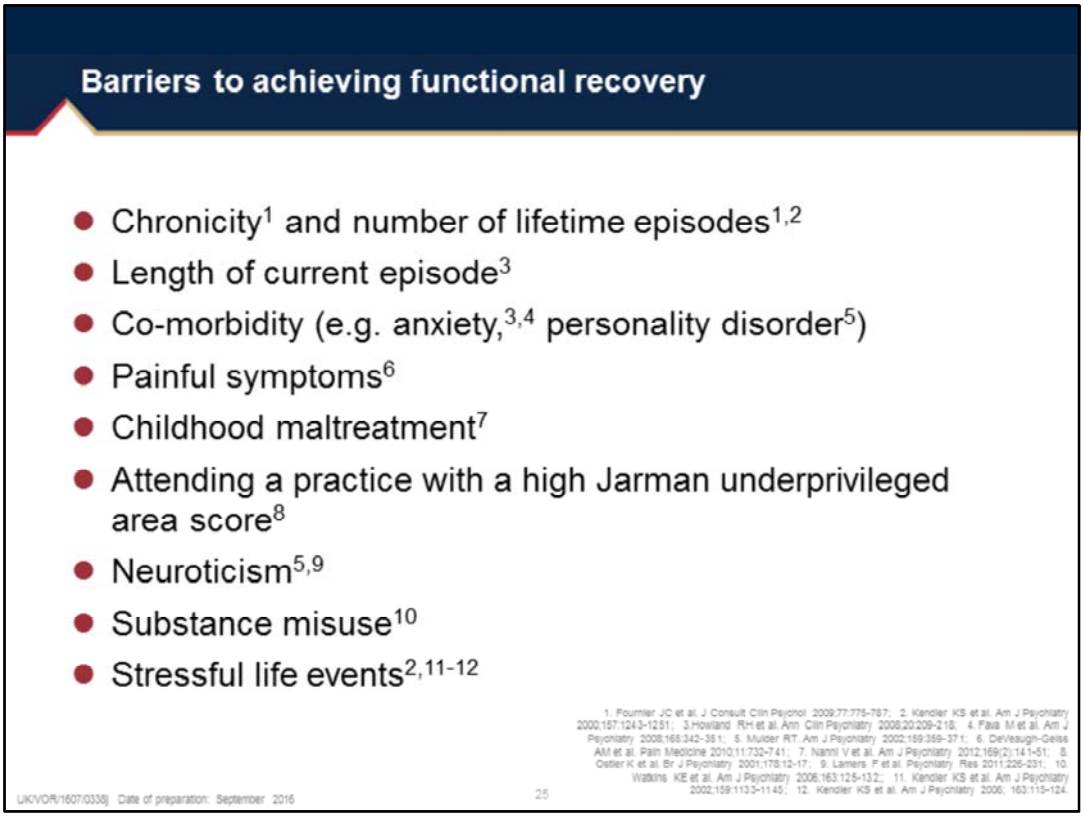
Assessment: patient factors



- Is diagnosis correct?
  - Bipolar
  - Emotionally unstable PD
- Comorbidity?
  - Psychiatric e.g. alcohol misuse, OCD
  - Physical e.g. hypothyroidism, chronic pain
  - Any comorbid disorder is a poor prognostic indicator for MDD
  - Successful treatment of comorbidity improves prognosis of MDD
  - Comorbidities require identification



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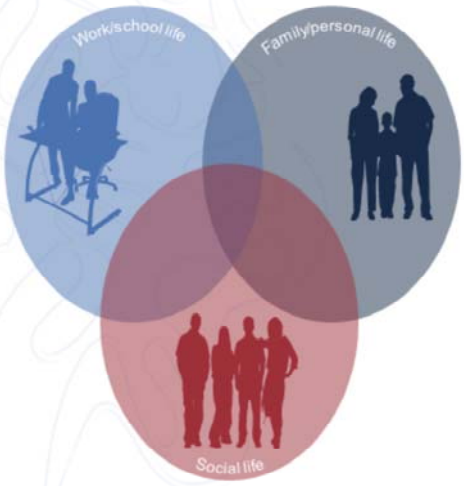
Assessment: patient factors



Social factors?

- Life events & chronic difficulties can precipitate and maintain MDD
- Identify and help the patient to address
- Promote effective coping strategies
- Discourage any that seem counter-therapeutic
- Consider social worker input
- Consider psychological treatment

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BAP Guidelines

Psychopharm

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

Anthony Cleare[1], CM Parlante[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[13], A Mallzia[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

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Abstract

A revision of the 2008 British Association for Psychopharmacology evidence-based guidelines for treating depressive disorders with antidepressants was undertaken in order to incorporate new evidence and to update the recommendations where appropriate. A consensus meeting involving experts in depressive disorders and their management was held in September 2012. Key areas in treating depression were reviewed and the strength of evidence and clinical implications were considered. The guidelines were then revised after extensive feedback from participants and interested parties. A literature review is provided which identifies the quality of evidence upon which the recommendations are made. These guidelines cover the nature and definition of depressive disorders, acute treatment with antidepressant drugs, choice of drug versus alternative treatment, practical issues in prescribing and management, next-step treatment, relapse prevention, treatment of relapse and stopping treatment. Significant changes since the last guidelines were published in 2008 include the availability of new antidepressant treatment options, improved evidence supporting certain augmentation strategies (drug and non-drug), management of potential long-term side-effects, updated guidance for prescribing in elderly and adolescent populations and updated guidance for optimal prescribing. Suggestions for future research priorities are also made.

Keywords

Antidepressants, depression, depressive disorder, treatment, evidence-based guidelines

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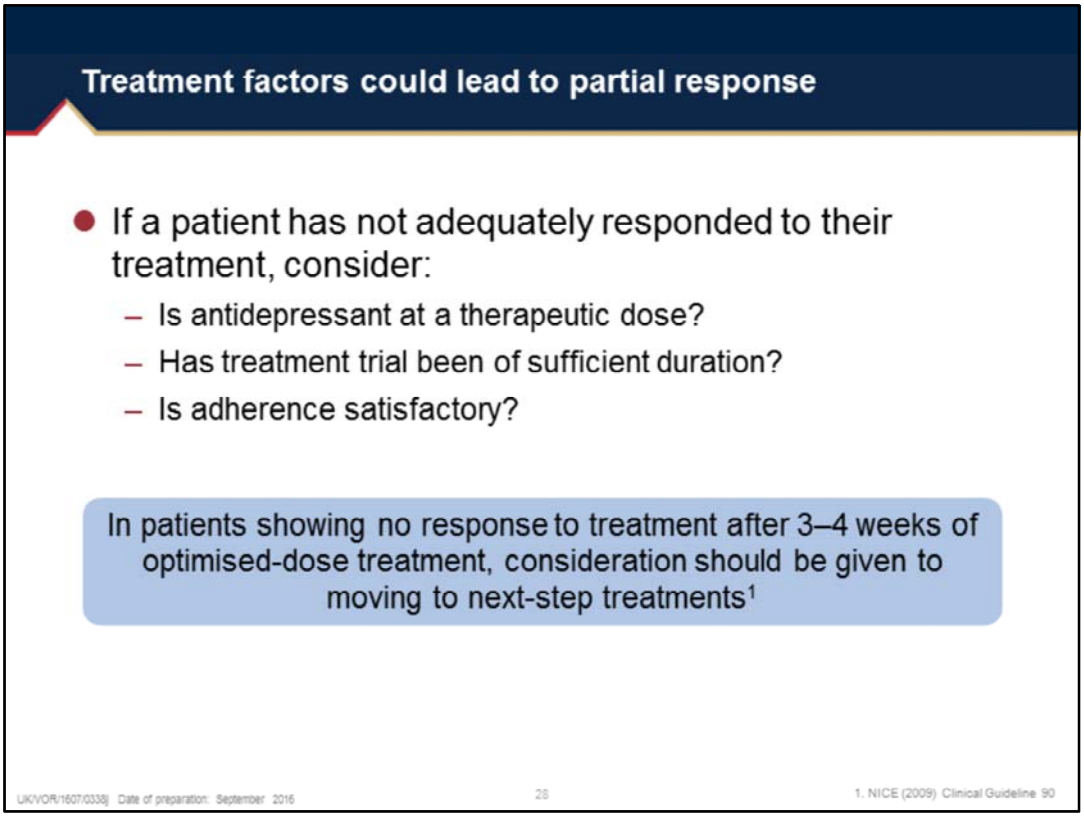

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1. NICE (2009) Clinical Guideline 90. Depression in adults: The treatment and management of depression in adults (update): full guideline

What is an adequate dose?

Not straightforward to answer; 2 questions to consider:

1.Has at least a minimally effective dose been given?

- See SPC for modern antidepressants
- Not clear for TCAs
- Traditionally defined as 125mg/day imipramine/ amitriptyline equivalent
- Lower TCA doses (⩽100 mg) superior to placebo in a meta-analysis[1]
- No efficacy benefit for higher doses but more drop outs[1]

2.Should the dose be increased?

- Most antidepressants have no good evidence for a dose response relationship
- A few do e.g. escitalopram and venlafaxine
- Always worth considering dose increase

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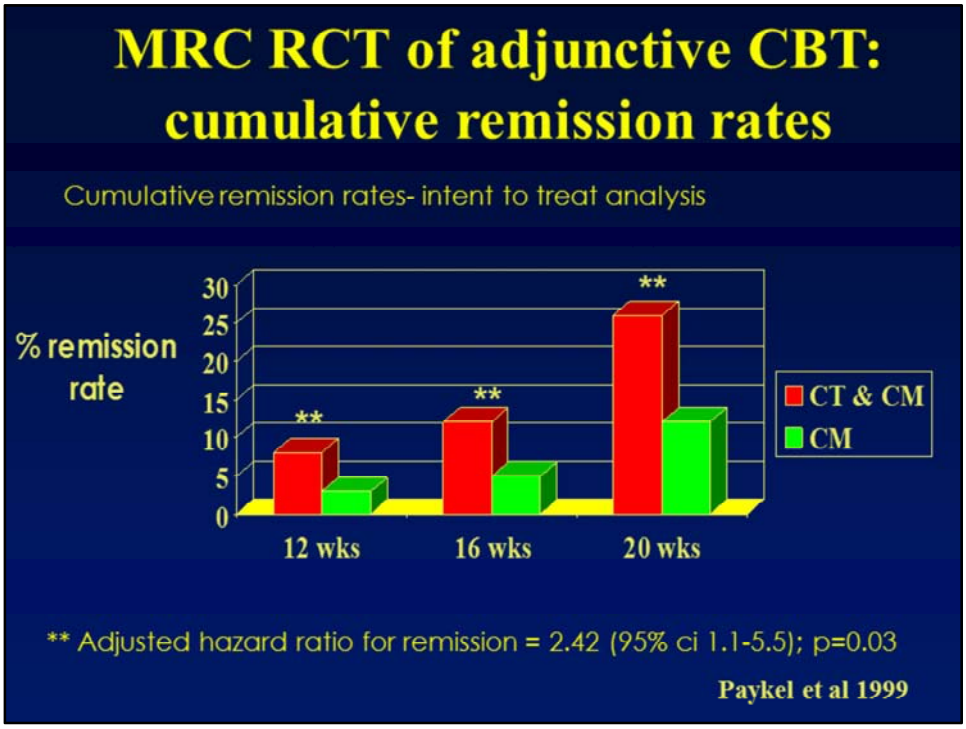


•Paykel, Scott, Teasdale, Cornwall, Jenaway, Garland, Moore, Hayhurst, Pope, Abbot, Johnson

•160 patients with residual symptoms of MDD >125mg Tricyclic ADM or equivalent for >8 wks HRSD -17 item >8 & BDI - 21 item >9

ADM plus CM
or
ADM plus CM plus 18 sessions of CT

Arch Gen Psychiatry. 1999 Sep;56(9):829-35.

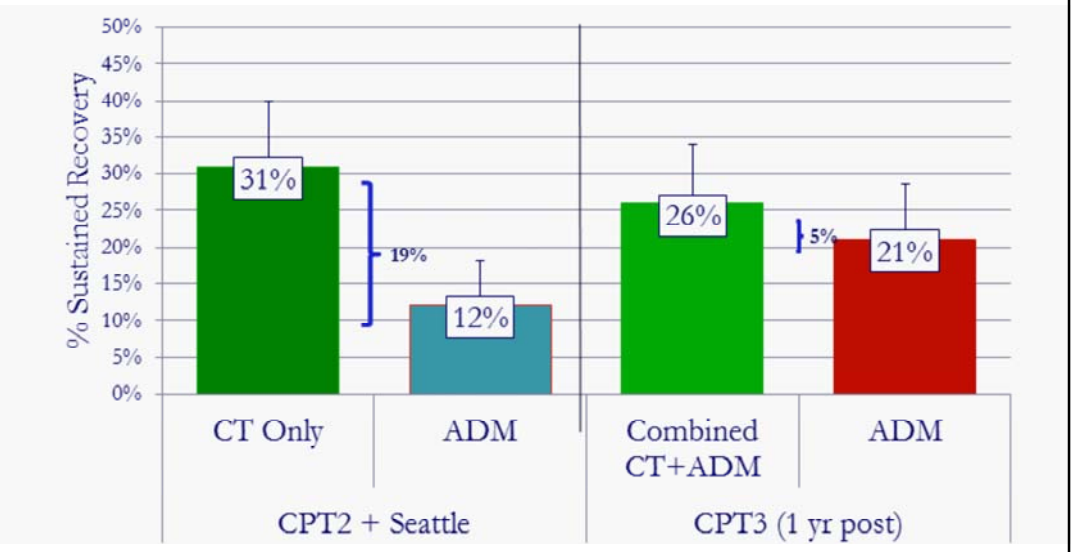
Prevention of relapse in residual depression by cognitive therapy: a controlled trial.

Paykel ES, Scott J, Teasdale JD, Johnson AL, Garland A, Moore R, Jenaway A, Cornwall PL, Hayhurst H, Abbott R, Pope M.

Department of Psychiatry, University of Cambridge, Cambridge, England.

BACKGROUND: Previous studies indicate that depressed patients with partial remission and residual symptoms following antidepressant treatment are common and have high rates of relapse. There is evidence that cognitive therapy may reduce relapse rates in depression. METHODS: One hundred fifty-eight patients with recent major depression, partially remitted with antidepressant treatment (mean daily doses equivalent to 185 mg of amitriptyline or 33 mg of fluoxetine) but with residual symptoms of 2 to 18 months' duration, were included in a controlled trial. Subjects were randomized to receive clinical management alone or clinical management plus cognitive therapy for 16 sessions during 20 weeks, with 2 subsequent booster sessions. Subjects were assessed regularly throughout the 20 weeks' treatment and for a further year. They received continuation and maintenance antidepressants at the same dose throughout. RESULTS: Cognitive therapy reduced relapse rates for acute major depression and persistent severe residual symptoms, in both intention to treat and treated per protocol samples. The cumulative relapse rate at 68 weeks was reduced significantly, from 47% in the clinical management control group to 29% with cognitive therapy (hazard ratio 0.54; 95% confidence interval, 0.32-0.93; intention to treat analysis). Cognitive therapy also increased full remission rates at 20 weeks but did not significantly improve symptom ratings. CONCLUSION: In this difficult-to-treat group of patients with residual depression who showed only partial response despite antidepressant treatment, cognitive therapy produced worthwhile benefit.

Sustained Recovery (1yr)



What is functional recovery?

- Functional recovery is more than looking well
- Return of clarity of thought
- Return of energy
  - so can undertake activities that the patient wants to
- All important elements of the patients life back to the way they were before episode of depression

"My everyday thinking became clearer and I could organise things in my mind more easily. It was like a pair of dirty glasses had been taken off and I could see again"

"I've also got my energy back"

"Work is going really well again and I have talked to my boss about putting in for a promotion"

NB – functional recovery will also reduce the risk of relapse

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Summary of options in partial responders

- Assessment; patient factors
  - Is diagnosis correct?
  - Are comorbidities present?
  - Consider social maintaining factors
- Assessment; treatment factors
  - Review antidepressant adherence
  - Has duration and dose been adequate?
- Pharmacological treatment options
  - Dose escalation
  - Switch to another antidepressant
  - Combination/augmentation treatments (e.g. Li, quetiapine XL)
  - Consider drugs to target key residual symptoms – sleep and cognitive.
- Psychological options: add CBT
- TMS/ECT

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Conclusions

- Goal – functional recovery
- Recognising partial response
  - Residual symptoms can be mood, cognitive or physical - **insomnia and cognitive deficits predominate and are most associated with poor functional recovery**
- Advise primary care on management of partial responders
- Have non-remission strategies
  - Instil (realistic) hope
  - Do something!!
  - Work systematically – **logical next pharmacological steps and CBT**

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