Implications of DSM-5 Mood Disorders for Future Treatment Efficacy Trials

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DSM-5 Timeline

- 2006 – workgroup recruitment
- 2007- workgroup and Task Force meetings – conference calls and face to face
- 2010 – posting of current thoughts on internet, consideration of feed back, changes, prepare for Field Trials.
- 2010-11 – Field Trials
- 2011 – review of Field Trial data – changes –present recommendations to Task Force
- 2012 – write text, layers of review
- 2013 – publish DSM-5

DSM-5 Process

- Appointment of workgroup chairs (13) and cross-cutting committees (culture-gender, developmental, instrumentation) by Drs. Kupfer and Regier
- Recruitment of workgroups, advisors, formation of subworkgroups (eg bipolar, unipolar, suicide, anxiety, PMDD)
- Biweekly workgroup and subworkgroup calls- face to face meetings every 6 months
- Development of standards for change – posting on internet, consider changes, test items for Field Trials
- Consider Field Trial results and input: Final recommendations
- Present recommendations to Task Force for approval.
- Write text, layers of review, ba-ba-ba-bing! **DSM-5**

Changes Currently Recommended in DSM-5 Mood Disorders

- Changes in Diagnostic Criteria: drop bereavement exclusion, add mixed specifier across bipolar disorder and MDD, separate psychosis from severity in MDD, drop antidepressant exclusion for mania lasting one week after stopping ADM. Specificity for NOS(CNEC). Drop post-partum depression???
- New Diagnoses: PMDD, mixed anxiety depression- sub-syndromal depression –anxiety, with significant impairment. TDD in children
- Change in Dysthymia to Chronic Depression ???
- Dimensions – Drop GAF for WHODAS II (pure impairment), add severity, anxiety severity, substance abuse severity.
- Suicide Assessment Guide – Amount of focus in management

Changes Proposed for MDD

- Drop bereavement exclusion – basis: other losses and stresses precede MDD – treatment outcome is similar. Argument: normal grief will be diagnosed as MDD – over treated
- Separate severity from psychosis specifier – basis: psychosis is not always severity
- Mixed specifier – basis 30-40% of MDD patients may have mixed manic/hypomanic features
- Drop post partum MDD? Basis – no evidence of increased risk. No evidence of risk period.- Problem: clinically important at very vulnerable time for mother and child

Bipolar Disorder

- Mixed specifier – no longer mixed state requiring full mania and full MDD. Basis- mixed features/dysphoric mania is seen across entire bipolar spectrum (BP II, NOS)
- Drop mania following ADM exclusion if mania persists one week after DC of ADM
- Bipolar NOS – Must specify xxx.1 too few symptoms, xxx.2 insufficient duration, xxx.3 hypomania only

Child Mood Disorders

- TDD – Temper Dysregulation and Disphoria – basis: overdiagnosis of child bipolar (MorenoC et al 2007), such children develop MDD/Anxiety Disorders, not bipolar (irritability is not enough)
- Self Injurious Behavior (SIB) – different management than suicidal behavior
- Suicidal Behavior risk assessment for children –David Shaffer

New Diagnoses Proposed

- Mixed Anxiety Depression – subsyndromal depression and anxiety (does not meet criteria for MDD or GAD – yet causes disability)- especially in primary care
- Premenstrual Dysphoric Disorder (PMDD) – basis: disability, separate from MDD
- Chronic Depression – replace dysthymia- basis: recall number of depressive symptoms over 2 years – Problems with MDD overlap
- Suicidal Behavior Disorder- basis high predictability, family-genetics, impulsiveness trait. Increase identification of risk. Problems: adequate criteria, does not help with assessment of acute risk.

Possible Opportunities for Outcome Measures

- Impairment-Disability: WHODAS II – "pure"measure – for caseness and outcome
- Measure of severity – PHQ-9 for MDE, and Altman for bipolar disorder
- Would a combination of disability and severity be useful outcome measures over time?
- Would mixed features predict poor outcome with ADM treatment for MDE?

What About Dimensional Measures?

- Anxiety severity – Predicts poor treatment response in STAR*D - Fava M et al, 2008, Thase M et al 2009
- Anxiety severity – Predicts higher suicide/attempt risk - Fawcett J et al 1990, Simon G 2007, Pfeiffer PN 2009
- Measuring anxiety outcome may be relevant in mood (and other disorders)
- Measuring substance abuse outcome may also be relevant.

Dimensions vs. Specifiers

- Dimensions – to estimate severity of non-criteria symptom that effects outcome. (eg severity of anxiety, level of concern for treatment required to reduce suicide risk, current severity of substance abuse)

- Specifier – To add characteristics to diagnostic criteria which may specify issues that are relevant for treatment outcome. (eg - psychotic, chronic, recurrent, severe, mixed features)

Anxiety Assessment –Psychic Anxiety – SADS-C

How much anxiety, fear, apprehension? How often? How bad does it get? Past week?

1- None

2- Slight, e.g., occasionally feels somewhat anxious

3- Mild e.g. often feels somewhat anxious

4- Moderate, e.g. most of the time feels anxious

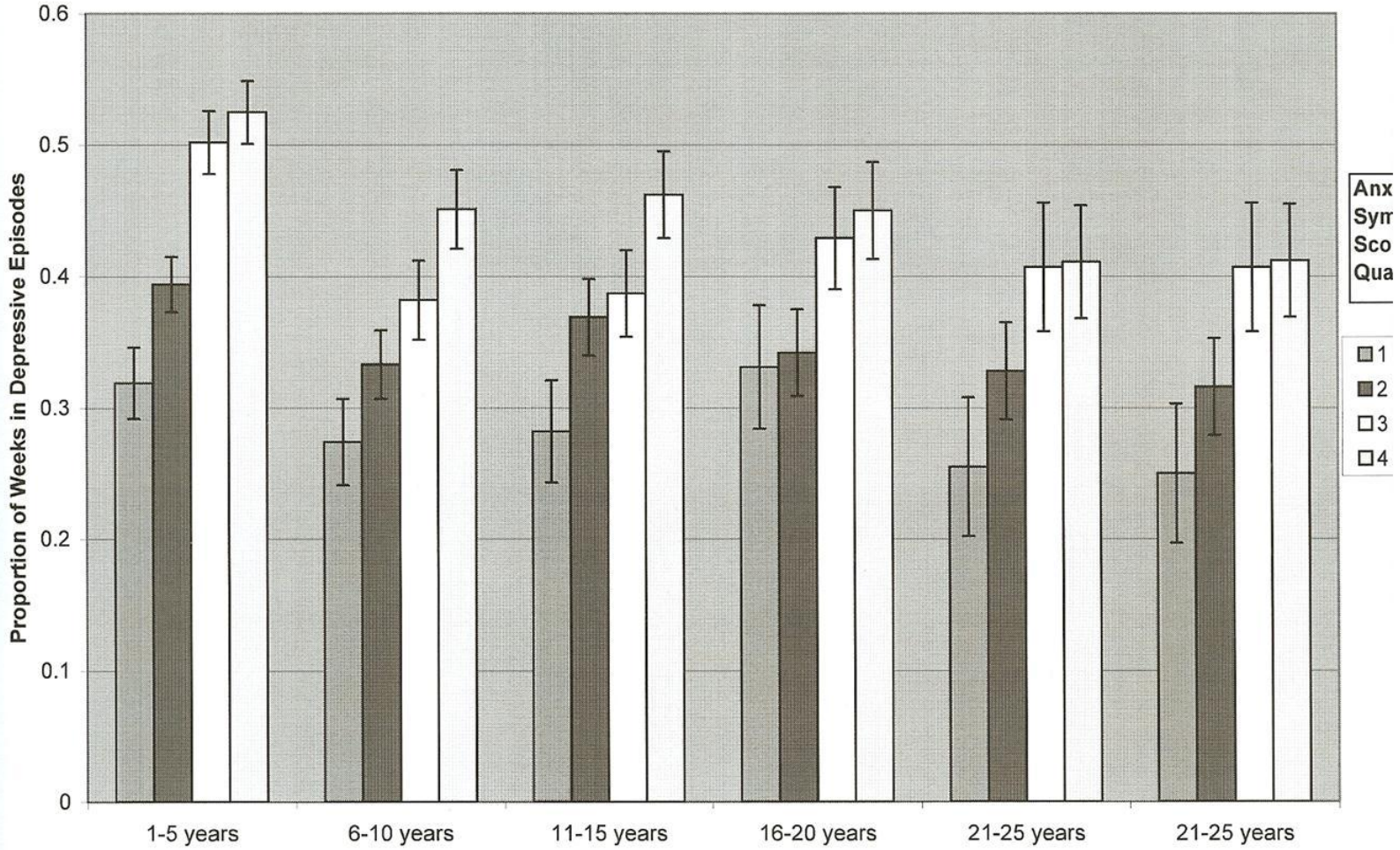
5- Severe e.g. most of the time feels very anxious- (ruminative- interferes with other thoughts)

6- Extreme e.g. pervasive feelings of intense anxiety

Distribution of Anxiety Summary Score

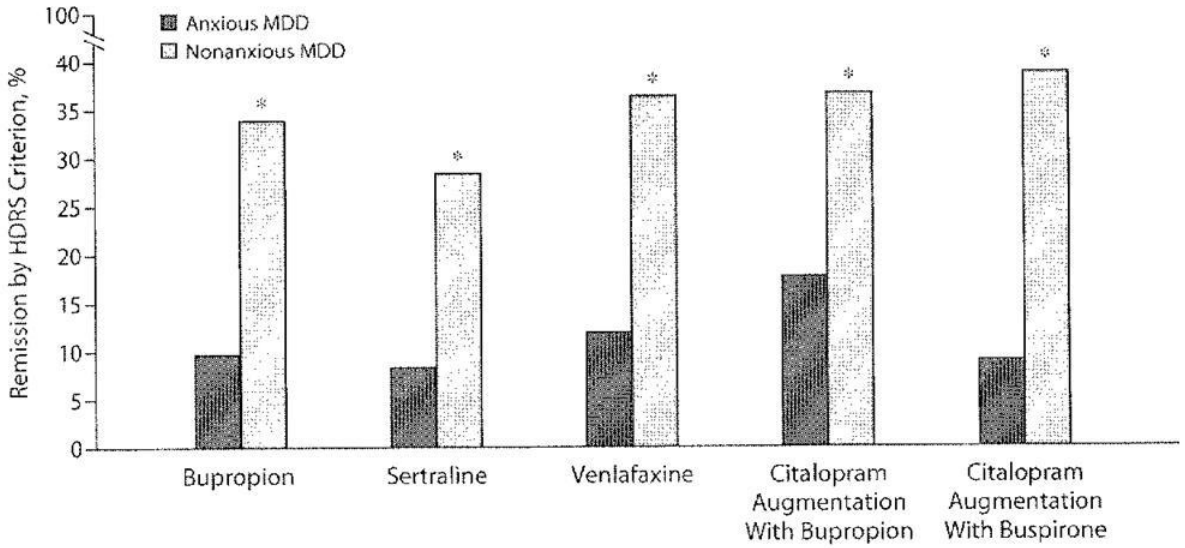
in 327 Unipolar Depressives

Baseline Anxiety Symptom Severity Levels and Mean (SE) Proportions of Weeks in Depressive Episodes by Follow-Up Period



longer period of treatment will be necessary in order to achieve full remission, and the greater the likelihood at any given time that the patient will still have too high a level of residual symptoms in order to be declared fully remitted, even if he or she has responded to treatment.

Figure 1. STAR*D Level 2 Remission Rates: Anxious vs Nonanxious Major Depressive Disorder[a]



[a]Data from Fava et al.[11]
*$P < .05$.
Abbreviations: HDRS = Hamilton Depression Rating Scale, STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

CONSEQUENCES OF INCOMPLETE REMISSION

Relapse rates following the citalopram phase of STAR*D showed that, compared with patients in remission, patients who ended the acute phase as responders without remission were about twice as likely to suffer a relapse during the first year after successful treatment, despite ongoing therapy.[10] The prognostic significance of obtaining complete remission can extend beyond the first year of follow-up: outcomes from a long-term, naturalistic study[12] of the course of MDD found that partial response was associated with a persistently increased risk of relapse or recurrence across a decade.

Prospective Study Findings- Standard Risk Factors May Not Predict Acute Risk, but Chronic Risk- Fawcett et al,1990

- **954 major affective disorder (>80% hosp)**
- **<u>First year follow up</u>- 13/34 suicides- standardized measures:**
  <u>no</u> significant difference between 13 suicides and 951 surviving:
  1.Severity of Suicidal Ideation-
  2.Hx Suicide Attempts (past and recent)
  3.Severity of Hopelessness
- **<u>Years 2-10</u> - significant correlation with suicide (34) compared with non-suicides**

Acute Suicide Risk Factors Fawcett et al, Am J Psychiatry,1990

- **Significantly more severe in suicides cf. non – suicides: weeks up to a year of follow up:**
- **Severity Psychic Anxiety(intensity + pervasiveness)**
- **Panic Attacks**
- **Global Insomnia (initiating, middle waking, early waking)**
- **Severity Anhedonia**
- **Alcohol Abuse (moderate-recent onset)**
- **Agitation (depressive turmoil)/ including mixed dysphoric mania)**

Inpatient Suicide - Clinical Features Within 1 Week n=76

Busch K. et al, J Clin Psych 2003

- **Severe Anxiety (SADS-C 5-6) 30%**
- **Severe Agitation 10%**
- **Both Severe Anxiety+Agitation 39%**
- **Either/Both 79%**
- **Anxiety/agitation (SADS-C <5) 22%**
- **Denial of Suicide Ideation 76%**
- **No harm contract 26%**

Co-Morbid Anxiety and Suicide in Bipolar Patients Simon G et al, 2007

- **>32,000 Bipolar Patient Data Base**
- **>Suicide and attempts (OR 1.8,1.4) : Male and Co-morbid Anxiety Disorder**
- **Suicide Attempts: Young and Substance Abuse**
- **Note different predictors: suicide vs. suicide attempts**
- **Only large N will reveal suicides vs attempts**

Anxiety as a Suicide Risk Factor in Depressed Veterans Pfeiffer PN et al, Depress Anxiety 2009

- **887,859 patients with depression**
- **Odds of suicide significantly increased in PD, GAD, Anx Nos (OR 1.25-7) Decreased in PTSD, no relationship with OCD,SP and others.**
- **Odd of suicide greater in patients receiving anti-anxiety medication (OR 1.71) and higher in those receiving high dose anti-anxiety medication (OR 2.26)**
- **Emphasize importance of co-morbid anxiety disorders and symptoms in increasing suicide risk in depressed patients.**
- **Suggests a relationship with anxiety severity**
- **It appears treatment of anxiety was not very effective.**

Anxiety Associated with Impulsivity in Bipolar Disorder Taylor CT et al, Anxiety Disord,2008

- Anxiety and Barratt impulsiveness scale in 114 outpatients with BD.
- Pts with comorbid anxiety disorder – significantly higher levels of impulsivity.
- Anxiety positively associated with impulsivity in patients with BD.

Nock Model of Suicidal Behavior Nock M et al,PLoS Med, 2009

- **Cross-national analysis of association among mental disorders and suicidal behavior:WHO World Mental Health Surveys**
- **108,664 respondents from 21 countries.**
- **Strongest predictors of SB in developed counties mood disorders, in undeveloped countries impulse-control disorders**
- **Large number of disorders predict suicide ideation – only disorders characterized by anxiety and impulse control disorders predicted suicidal behaviors in both developed and undeveloped countries.**
- **Model: Low mood – Suicidal Ideation. Increased anxiety/impulsiveness leads to Suicidal Behavior**

Suicide Assessment-Risk Factor Groups

- **Any history of suicide attempt.**
- **Tendency to lose temper or become aggressive with little provocation.**
- **Family History of suicide attempts or suicide**

- **Living alone, chronic severe pain, or recent (past 3 months) loss**
- **Recent psychiatric admission/discharge or first diagnosis of MDD, bipolar disorder of schizophrenia**

- **Recent increase alcohol abuse or worsening of depressive symptoms**
- **Current (past week) preoccupation with or plans for suicide**
- **Current psychomotor agitation, marked anxiety, or hopelessness**

Scoring of Risk Items

- 0 – Lowest concern
- 1- Some concern
- 2- Moderate concern
- 3- High concern
- 4- Very high concern

Other "Personality Dimensions" May More Comprehensively Measure Outcome

- Paroxetine treatment reduced neuroticism (by NEO) after controlling for depression vs. placebo- 6.8x (.001) and increased extroversion- 3.5x (.002).
- Advantage of paroxetine over placebo no longer significant after controlling for change in neuroticism.
- No change for placebo or CBT after controlling for depression. Tang TZ et al, 2009
- Neuroticism reduction predicted lower relapse rates. Also found by Weissman M, and Klerman G 1981
- What about impulsivity severity? It may relate to anxiety severity

A Plea for More Effective Treatments

- RCTs are needed for promising candidates that are not sponsored by Pharmaceutical Companies.
- Emerging data suggests that ADM are not as effective in bipolar depression.
- More effective treatments for co-morbid anxiety are needed
- Examples: ketamine, pramipexole, modafinil, prazosin, n-acetyl cysteine, SAMe etc- especially in treatment resistant depression/bipolar depression

Ketamine – a new paradigm?

1. 18 subjects with treatment resistant bipolar depression infused with ketamine (0.5 mg/kg) or placebo. 2 weeks apart. Response significant in 40 minutes, 71% ketamine vs, 6% placebo, significant through day 3, effect size .52, effect size .8 day 2. Dizgranados N et al,2010--2.33 subjects, 10- SSI score of 4 or more, had decrease 40 minutes – 4 hrs after infusion Dizgranados et al, 2010

3. 2 hospice patients – depressed/anxious – ketamine orally (0.5 mg/kg) – rapid response lasting 2-4 weeks.Irwin SA, Inglewicz A J Palliat. Med 2010

Modafinil

- 85 patients – bipolar depression on mood stabilizers. Modafinil (m= 177mg) response/remission 43%/39% vs placebo 23%/18% Frye M et al, 2007
- Armodafinil – bipolar depression despite olanzapine/valproic acid – 150 mg vs placebo, N=128, numerical difference NS in depression
- Armodafanil – 200 mg in OSA with MDD – improved sleepiness, but not mood on QIDS. Krystal AD et al, 2010
- Limited treatment options in bipolar depression beg more controlled studies.

Pramipexole

- Aiken review: 24 reports reviewed and effect size calculated: effect sizes of 0.6 – 1.1 in both bipolar and unipolar depression.
- Short term mood switching: 1% mania, 5% hypomania Long Aiken C, J Clin Psychiatry 2007.
- Long term follow-up 16 cases- 6.7 +/- 9.0 months: For all patients significant improvement in depression beginning at 4 weeks – up to 36 weeks. 50% stopped medication in 2 months. No change in mania ratings for up to 9 months. El-Mallakah RS et al, Psychiatr Q 2010.
- With limited treatment options for bipolar/resistant depression – further studies are needed.

Prazosin

- Anxiety is common in bipolar and unipolar MDE – it predicts poor outcome and suicide – treatment options are limited.
- Prazosin was found to ameliorate combat trauma nightmares in four cases Raskind MA et al, J Clin Psychiatry 2000, then in an RCT n=40, Raskind MA et al, Biol Psychiatry 2007
- Daytime psychological distress in civilian trauma Taylor FB et al, Biol Psychiatry 2006
- Agitation/aggression in Alzheimers Wang LY et al, Am J Geriatr Psychiatry 2009
- Effectiveness for nightime symptoms cf quetiapine, 61% with twice the discontinuation rate for quetiapine 34%. Byers MG et al. J Clin Psychopharmacol 2010

Summary

- DSM-5 changes will not pose problems for trial designs.
- Addition of dimensions in DSM-5 may present new opportunities to study a broader array of meaningful treatment outcomes.
- We need more effective treatments for bipolar and Rx resistant depression.
- We need studies of comorbid severe anxiety treatments in mood disorders.