DSM-5 and mood disorders: The Good, the Bad and the Ugly

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Disclosures

Speaker bureau :	Astra Zeneca	Biovail
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Janssen-Ortho	Lundbeck	(GSK)
Sunovion	Otsuka	Organon
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FISHING POX

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SYMPTOMS — Continual complaint as to need for fresh air, sunshine and relaxation. Patient has blank expression, sometimes deaf to wife and kids. Has no taste for work of any kind. Frequent checking of tackle catalogues. Hangs out in Sporting Goods Stores longer than usual. Secret night phone calls to fishing pals. Mumbles to self. Lies to everyone.

Expert diagnosis and treatment at any Canadian Tire Corporation Tackle Bar.

NO KNOWN CURE

Quarantine unnecessary

TREATMENT --- Medication is useless. Disease is not fatal.

Victim should go fishing as often as possible.

Visit your local CANADIAN TIRE CORP. ASSOCIATE STORE for the "BEST" in fine Fishing Tackle.

THE LANCET

Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

Cross-Disorder Group of the Psychiatric Genomics Consortium

The Lancet - 28 February 2013









Figure 1: Manhattan plot of primary fixed-effects meta-analysis

Horizontal line shows threshold for genome-wide significance (p<5×10").



Figure 3: Pair-wise cross-disorder polygene analysis

We derived polygene risk scores for each disorder (discovery sets) and applied them sequentially to the remaining disorders (target sets). Results are grouped by each discovery set. Each pair is shown on the x-axis and the proportion of variance explained for the target disorder (estimated via Nagelkerke's pseudo R^2) on the y-axis. For purposes of illustration, three p_T cutoffs are shown, but appendix p 62 shows the proportion of variance results for a broader range of cutoffs. p_T =training-set p value (used to select training set SNPs). Significance of results: a=p<0.05; $b=p<10^{-4}$; $c=p<10^{-16}$; $d=p<10^{-16}$; $f=p<10^{-50}$. ADHD=attention deficit-hyperactivity disorder. ASD=autism spectrum disorders. BPD=bipolar disorder. MDD=major depressive disorder.

Young at heart.Slightly older in other places.







From DSM-IV to DSM-5: Depressive disorders

- The <u>bereavement</u> exclusion in DSM-IV was removed from <u>depressive</u> disorders in DSM-5.
- New <u>disruptive mood dysregulation disorder</u> (DMDD) for children (from 6 up to 18 years).
- <u>Premenstrual dysphoric disorder</u> moved from an appendix for further study, and became a disorder.
- Specifiers were added for mixed symptoms and for anxiety, along with guidance to physicians for suicidality.
- The term dysthymia now also would be called persistent depressive disorder.





Major Depressive Disorder

- Recurrence : (single Episode /recurrent)
- Severity : (mild/moderate/severe)
- With psychotic features
- Remission (in partial or in full remission)
- And then as many specifiers that apply to the current episode:
 - with anxious distress / with mixed features/ with melancholic features / with atypical features / with mood-congruent psychotic features / with moodincongruent psychotic features / with catatonia / with peripartum onset / with seasonal pattern







<u>Disruptive Mood Dysregulation</u> <u>Disorder</u> (DMDD)

A. Severe recurrent temper manifested verbally (e.g., verbal rages) and/or behaviorally (e.g., physical aggression towards people or property) that are grossly out of proportion in intensity or duration to the situation or provocation.

B. The temper outbursts are inconsistent with developmental level.

C. The temper outbursts occur, on average, three or more times per week.

D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observable by others (e.g., parents, teachers, peers).

E. Criteria A-D have been present for 12 or more months. Throughout that time, the individual has not had 3 or more consecutive months without all the symptoms in Criteria A-D.

F. Criteria A or D is present in at least two of the three settings (i.e. at home, at school, with peers) and are severe in at least in one these.

G. The diagnosis should not be made for the first time before age 6 or after age 18.





(...Continued)

H. By history or observation, the age at onset of Criteria A-E is before age 10 years.I. There has never been a distinct period lasting more than one day during which the full symptom criteria, except duration, for a manic or hypomanic episode have been met.

Note: Developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation, should not be considered as a symptom of mania or hypomania.

J. The behaviors do not occur exclusively during an episode of Major Depressive Disorder and are not better accounted for by another mental disorder (e.g., Autism Spectrum Disorder, Posttraumatic Stress Disorder, Separation Anxiety Disorder, Persistent Depressive Disorder Dysthymic Disorder).

Note: This diagnosis cannot co-exist with Oppositional Defiant Disorder, Intermittent Explosive Disorder, or Bipolar Disorder, though it can co-exist with others, including Major Depressive Disorder, Attention Deficit/Hyperactivity Disorder, Conduct Disorder, and Substance Use Disorders. Individuals whose symptoms meet criteria for both DMDD and Oppositional Defiant Disorder should only be given the diagnosis of DMDD. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of DMDD should not be assigned.

K. The symptoms are not attributable to the physiological effects of a substance or to another medical or neurological condition







Disruptive Mood Dysregulation Disorder (DMDD)

• No specifiers.







DMDD: rationale and limitations

- Youths with chronic irritability and anger outbursts are being increasingly misdiagnosed as having bipolar disorder¹
- Scientific support came from Severe Mood Dysregulation (SMD) which is not identical to DMDD (eliminating hyperarousal as a criterial symptom and age at onset of 10)
- No justification associated with the age of diagnosis > 6
- It is unclear which aspects of the pathophysiology are unique to DMDD and which are shared with the individual emotional and behavioral disorders wth which it so commonly occurs.

- 1. Leibenluft E: Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatry 2011; 168:129–142.
- 2. Copeland WE; Angold A; Costello EJ; Egger H: Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. Am J Psychiatry 2013; 170:173–179.







Persistent Depressive Disorder (previously Dysthymia)

This disorder represents a consolidation of DSM-IV-defined chronic major depressive disorder and dysthymic disorder.

A. 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 one year.

B. 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.

C. During the two-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 the time.

D. Criteria for a MDD may be continuously present for 2 years.







(...Continued)

E. There has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder.

F. The disturbance in not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other psychotic disorder.

G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism)

H. The symptoms cause a clinical significant distress or impairment in social, occupational, or other important areas of functioning.

Note: Because the criteria for a MDE include four symptoms that are present from the symptom list for persistent depressive disorder, a very limited number of individuals will have depressive symptoms that have persisted longer than 2 years but will not meet criteria for persistent depressive disorder. If full criteria for a MDE have been met at some point during the current episode of illness, they should be given a diagnosis of MDD. Otherwise, a diagnosis of other specified depressive disorder or unspecified depressive disorder is warranted.





Persistent Depressive Disorder (previously Dysthymia)

• Specify if:

- With anxious distress / with mixed features/ with melancholic features / with atypical features / with mood-congruent psychotic features / with mood-incongruent psychotic features / with peripartum onset
- In partial remission / in full remission
- Early onset (before age 21) / Late onset
- With pure dysthymic syndrome / with persistent MDE / with intermittent MDE, with current episode / with intermittent MDE, without current episode.
- Current severity: Mild / Moderate / Severe





Gradations of "Mixedness"



"Mixed Depression" or "Depressive Mixed States"

STEP-BD: Presence of sub-syndromal mania (1-3 mania symptoms) is frequent during index bipolar MDE



Longitudinal Course of Bipolar Disorder

- Prospective follow-up of 219 BDI patients — 122 (56%) followed for ≥20 years
- 1208 episodes observed
 - Only 2 pure mixed episodes (<1%)
 - Defined as concurrent depression and mood elevation throughout the entire episode
 - 94 episodes (8%) of "mixed major cycling"
 - Episode of major cycling that at some point included a mixed state of concurrent depression and mood elevation



Mixed States: Diagnostic Complexities

- There is concordance among many researchers that mixed states are not simply a simultaneous or sequential occurrence of affective symptoms of opposite polarity, i.e., depression and mania, but rather complex, fluctuating and unstable clinical pictures¹
- This may not be captured by DSM-IV criteria alone which operationalizes mixed states as a stable construct.
- Mixed states may be better defined along a continuum/spectrum (consistent with clinical practice) as opposed to being a static/modal phenomenon
- The "degree of mixity" becomes the operational term

1. Kruger S, et al. Bipolar Disorders 2005: 7: 205-215.









Bipolar Disorders Classification

296.4X / 296.5X

296.89

301.13

291.89 / 292.84

293.83

296.89

296.80

Bipolar I Disorder Bipolar II Disorder Cyclothymic Disorder Substance-Induced Bipolar Disorder Bipolar and Related Disorder Due to Another Medical Condition Other Specified Bipolar and Related Disorder Unspecified Bipolar and Related Disorder







Bipolar I Disorder (296.4X or 296.5X)

 Type of current or most recent episode ; his status with respect to current severity, presence of psychotic features and remission status.

Bipolar I	Current or most recent episode manic	Current or most recent episode hypomanic	Current or most recent episode depressed	Current or most recent episode unspecified	
Mild	296.41	NA	296.51		
Moderate	296.42	NA	296.52		
Severe	296.43	NA	296.53		







Bipolar I Disorder (296.4X or 296.5X)

Bipolar I	Current or most recent episode manic	Current or most recent episode hypomanic	Current or most recent episode depressed	Current or most recent episode unspecified	
With psychotic features	296.44	NA	296.54	NA	
In partial remission	296.45	296.45	296.55	NA	
In full remission	296.46	296.46	296.56	NA	
Unspecified	296.40	296.40	296.50	NA	







Bipolar I Disorder (296.4X or 296.5X)

- Specify if:
 - With anxious distress
 - With mixed features
 - With rapid cycling
 - With melancholic features
 - With atypical features
 - With mood-congruent psychotic features

- With mood-incongruent psychotic features
- With catatonia (293.89)
- With peripartum onset
- With seasonal pattern







Bipolar II Disorder (296.89)

- Specify current or most recent episode:
 - Hypomanic or Depressed
- Specify if:
 - With anxious distress
 - With mixed features
 - With rapid cycling
 - With mood-congruent psychotic features
 - With mood-incongruent psychotic features
 - With catatonia (add 293.89)

- With peripartum onset
- With seasonal pattern
- Specify course if full criteria for a mood episode are not currently met:
 - In parital remission or In full remission
- Specify severity if full criteria for a mood episode are currenlty met:
 - Mild / Moderate / Severe







Other Specified Bipolar and Related Disorder (296.89)

- Short-duration hypomanic Episodes (2-3) & MDEs
- MDEs & Hypomanic Episodes characterized by insufficient symptoms
- Hypomanic Episode witout MDE
- Short Duration (less than 2 years) Cyclothymia
- * Uncertain Bipolar Condtions







Proposed revision on Bipolar Disorder diagnostic category (2/3)

Bipolar Disorder not Elsewhere Classified (NEC)

- Subclassification will be used for this diverse group of conditions.
- The recorded name of the condition should NOT be "Bipolar Disorder NEC" but rater, one of the following diagnostic terms:







Proposed ICD – 11 Mood Disorders Classification

F30 First manic episode F31 Bipolar affective disorder F32 First depressive episode F33 Recurrent depressive disorder F34 First mixed affective episode F35 Persistent mood disorders F38 Other mood disorders F39 Unspecified mood disorders







Three-Fold Higher Rate of Bipolar Disorder Amongst Individuals with MDD When Using Bipolar Specifier

Table 1. Demographic Features of the Study Sample

					No. (%)		
Country	Patients, No.	Hospitalized, %	Age, Mean (SD), y	Male Sex, %	l Bipolar <i>DSM-IV-TR</i>	Bipolar Specifier	
Bosnia	200	46.5	46.3 (10.9)	32.5	45 (22.5)	111 (55.5)	
Bulgaria	300	46.0	49.8 (12.5)	36.5	56 (18.7)	171 (57.0)	
China	727	45.9	39.7 (14.4)	39.1	105 (14.4)	290 (39.9)	
Egypt	306	24.2	37.7 (12.8)	49.0	42 (13.7)	144 (47.1)	
Georgia	254	18.5	46.5 (15.0)	32.9	39 (15.4)	103 (40.6)	
Germany	251	59.4	48.0 (12.3)	36.8	29 (11.6)	102 (40.6)	
Iran	313	37.4	38.4 (12.3)	33.9	57 (18.2)	169 (54.0)	
Korea	212	25.5	45.0 (14.5)	27.8	15 (7.1)	55 (25.9)	
Macedonia	224	26.8	47.5 (13.3)	28.6	29 (12.9)	107 (47.8)	
Morocco	317	20.8	39.7 (11.5)	38.3	55 (17.4)	148 (46.7)	
The Netherlands	220	12.7	46.1 (13.7)	40.0	28 (12.7)	81 (36.8)	
Pakistan	265	37.0	38.2 (12.0)	50.4	60 (22.6)	158 (59.6)	
Portugal	311	11.9	45.9 (13.0)	25.7	45 (14.5)	172 (55.3)	
Slovakia	297	57.6	48.4 (13.2)	38.0	50 (16.8)	166 (55.9)	
Spain	655	25.5	47.2 (13.9)	33.1	100 (15.3)	324 (49.5)	
Taiwan	420	14.8	45.3 (12.7)	27.2	64 (15.2)	149 (35.5)	
Ukraine	297	73.7	46.9 (13.1)	29.6	65 (21.9)	156 (52.5)	
Vietnam	66	37.9	40.7 (11.1)	51.5	19 (28.8)	41 (62.1)	
Total	5635	34.4	44.1 (13.7)	35.5	903 (16.0)	2647 (47.0)	

Angst J. et al. Arch Gen Psychiatry. 2011;68(8):791-799.







Patients With Mixed Episodes Have Poor Treatment Outcomes

- More severe course of illness^{1,2}
- Less frequent remission/higher risk of reoccurrence^{1,2}
- More substance abuse^{1,2}
- Poorer response to some medications²
- Increased risk of suicide^{3,4}
- 1. Shah NN, et al. *Psychiatr Q.* 2004;75(2):183-196. 2. Prien RF, et al. *J Affect Disord.* 1988;15(1):9-15.
- 3. Hirschfeld RMA, et al. *J Clin Psychiatry.* 2003;64(1):53-59. 4. Goldberg JF, et al. *J Affect Disord.* 1999;56(1):75-81.







Certificate of Analysis from DR. JOHN MUTER, F.R.S.E., Past President of the Society of Public Analysis; Editor of the "Analysis"; Author of "Manuals of Analytical and Pharmaceutical Chemistry and of Materia Method" "I have examined SALT REGAL with the following results : That it is an effervescent saline, compounded from absolutely pure ingredients. When it is placed in contact with water, the "I have examined SALL MEAN is in the formation of two of the best known saline aperients, and in addition to these there is also developed a small quantity of an oxidising chemical combination which ensues results in the vater used disinfectant tending to destroy any impurities present in the water used. "I have not before met with a so well manufactured and ingenious combination, at once perfectly safe and yet so entirely efficient for the purposes for which it is recommended."-JOHN MUTER. HITA PATENT RIGHTS HER MAJESTY'S PROTECTED THROUGHOUT THE WORLD. ROYAL LETTERS PATENT. An Appetising and Refreshing Tonic. A Thirst-Quencher for all occasions. A morning "Pick-me-up." A high-class Effervescing, Antiseptic Salt, develops Ozone, the Principle of Life. Prevents and Relieves FLATULENCE, Nausea, GIDDINESS, Heartburn, Acidity, Palpitation, Bilious HEADACHE, Dyspepsia, Fevers, Malaria, Irritation of the Skin, Liver Complaint, Lassitude, WEARINESS, &c. Corrects all Impurities arising from Imparts New Life and Vigour errors of diet, eating, or drinking. to the System. The Editor of "HEALTH," the great Authority of HYGIENE, recommends SALT REGAL for general use in Families, and speaks in the highest praise of SALT REGAL. FOR PURITY, FOR SAFETY, FOR EXCELLENCE, For MARKED DISTINCTION from Saline Preparations in which Alkaline clements, so irritating to the Digestive Organs, unduly predominate. Lieut.-Colonel HUGH BAMBER, Margate, says :-"I have now used SALT REGAL for two years. I have found it the pleasantest and most agreeable in taste of all Salines, and a certain cure for bilious headache and furred

STRENUOUSLY REFUSE!

tongue, from whatever cause arising."

To have old-fashioned, worn-out Salines palmed off upon you. Insist upon having SALT REGAL, which imparts new life to the system, develops ozone, the principle of life, and turns to a beautiful rose pink colour when mixed with water. The enormous sale of SALT REGAL testifies to its superiority and excellence over all other remedies for Dyspepsia, Flatulence, Headache, and kindred complaints.

SALT REGAL may be obtained of all Chemists, and at the Stores; but if any difficulty, send 2/9 addressed to the Manager, Salt Regal

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A CLEAR HEAD.













EDITORIAL

Why are there no treatment guidelines for mood disorders and comorbidities?

Raymond W. Lam, MD, FRCPC Executive Chair, Canadian Network for Mood and Arxitely Treatments (CANMAT) Mood Disorders Centre University of British Columbia Vancouver, British Columbia, Canada

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Lakshmi N. Yatham, MBBS, FRCPC, MRCPsych (UK) Bipolar Chair, CANMAT Department of Psychiatry University of British Columbia Vancouver, British Columbia, Canada ood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are among the most prevalent and burdensome medical conditions. In a World Mental Health Survey sponsored by the World Health Organization, the lifetime and 12-month prevalence rates for these 2 disorders in 17 developed and developing countries¹ were 12.5% and 5.6% for major depressive episodes, respectively, and 1% and 0.7% for BD, respectively.² A recent commentary on challenges in global mental health identified depression as the third leading contributor to the global disease burden; unipolar depressive disorders and BD, respectively, were ranked first and fourth in an evaluation of the global burden across all mental, neurological, and substance use disorders.³ Previous studies have highlighted the enormous unmet need for treatment among persons with mood disorders.⁴

Comorbidity has been defined as "any distinct additional clinical entity that has coexisted or may occur during the clinical course of a patient who has the index disease under study."⁵ This may apply equally to ≥ 2 physical diseases, ≥ 2 mental disorders, or the co-occurrence of mental and physical disorders. Comorbidity is prevalent among persons with mood disorders. In developed countries, 62% of persons identified

- Comorbidity is the rule, not the exception
- Many possible combinations of comorbidities
- Few high quality studies to guide treatment decisions

SANTÉ MENTALE

 Clinicians still request guidance for treatment options

	Comorbid DSM-IV Disorder	Comorbid Chronic Physical Disorder		
Major Depression	62%	72%		
Bipolar Disorder	88%	59%		
Merikangas et a	al, 2010; al, 2011.			



CANMAT Clinical Guidelines







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CANMAT Task Force Recommendations for Mood Disorders and Comorbid Conditions

- Roger McIntyre, Ayal Schaffer, Serge Beaulieu
- Published February, 2012
- Anxiety, medical, personality, substance use, ADHD, metabolic syndrome
- Available at www.canmat.org









"Nearly all genetic factors identified thus far... seem to confer somewhat comparable risk for schizophrenia and bipolar disorder and, perhaps, for other disorders such as unipolar depression, substance abuse, and even epilepsy."

"... the biology of psychotic illnesses may fail to align neatly with the classic Kraepelinian distinction between schizophrenia and manic-depressive illness... However, they do resonate with clinical observations that many patients present with a mix of bipolar and schizophrenia symptoms, both at a single admission and also across time."

B.N. Cuthbert and T.R Insel. Schizophrenia Bulletin. 2010. 36 (6): 1061-1062.







Arguments en faveur d'une classification dimensionnelle

"These clinical observations support the accelerating body of literature over the last decade arguing that Kraepelin's classic dichotomy for psychotic disorders may need to be superseded by a new system based on biology as well as observed clinical phenomenology."

B.N. Cuthbert and T.R Insel. Schizophrenia Bulletin. 2010. 36 (6): 1061-1062.







Research Domain Criteria

	Units of analysis							
Domains/constructs	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-reports	Paradigms
Negative valence systems								
Active threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive valence systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for social processes								
Imitation, theory of mind								
Social dominance								
Facial expression identification								
Attachment/separation fear								
Self-representation areas								
Arousal/regulatory systems								
Arousal and regulation (multiple)								
Resting state activity								

La Théorie,

c'est quand on comprend tout et que **rien** ne marche.

La Pratique,

c'est quand tout marche, mais On ne sait pas pourquoi.

Ici

nous avons réussi les deux : rien ne marche

et personne ne sait pourquoi.

In many of the results of randomized clinical trials or of risk studies that use categorical measures, **a** report of statistical non-significance may be partially or wholly due to the lack of power to detect effects due to use of categorical measures, particularly when the cutoff defining the categorical measures is set by intuition rather than optimally based on empirical evidence.

Kraemer, HC. Int J. Methods in Psych. Res. 2007. 16 (S1): S8-S15.







Approche empirique

 Permet des analyses statistiques plus ciblées sur les modérateurs et médiateurs donc plus en harmonie avec les stratifications cliniques

 Rapprochement avec les symptômes cliniques observés par les cliniciens et vécus par les patients

 Pourrait donc éventuellement créer une classification plus écologiquement valide

Kraemer, HC. Int J. Methods in Psych. Res. 2007. 16 (S1): S8-S15.







- Meilleure modélisation de la psychopathologie dans des modèles animaux
- Approche qui favorise l'étude de l'aspect dévelopmental des maladies







- Faibles validités inter-juges (Kappa ratings) obtenues lors des essais en milieux cliniques (même académiques)
- Dépression: 0.34 !!!!







 Risquons de devoir redéfinir l'ensemble des traitements en fonction des nouveaux critères







DSM-5 update

- DSM-5 will move to a nonaxial documentation of diagnosis, combining the former Axes I, II, and III, with separate notations for psychosocial and contextual factors (formerly Axis IV) and disability (formerly Axis V)
- Incorporation of a developmental approach to psychiatric disorders
- harmonization of the text with ICD
- integration of genetic and neurobiological findings by grouping clusters of disorders that share genetic or neurobiological substrates
- recognition of the influence of culture and gender on how psychiatric illness presents in individual patients
- introduction of dimensional assessments
- DSM-5 not DSM-V: new updates will be possible without waiting for DSM-6!





I can only please one person per day . today is not your day. tomorrow doesn't look good either





