

Why DSM-5 should have returned to Kraepelin's concept of Manic Depressive Illness

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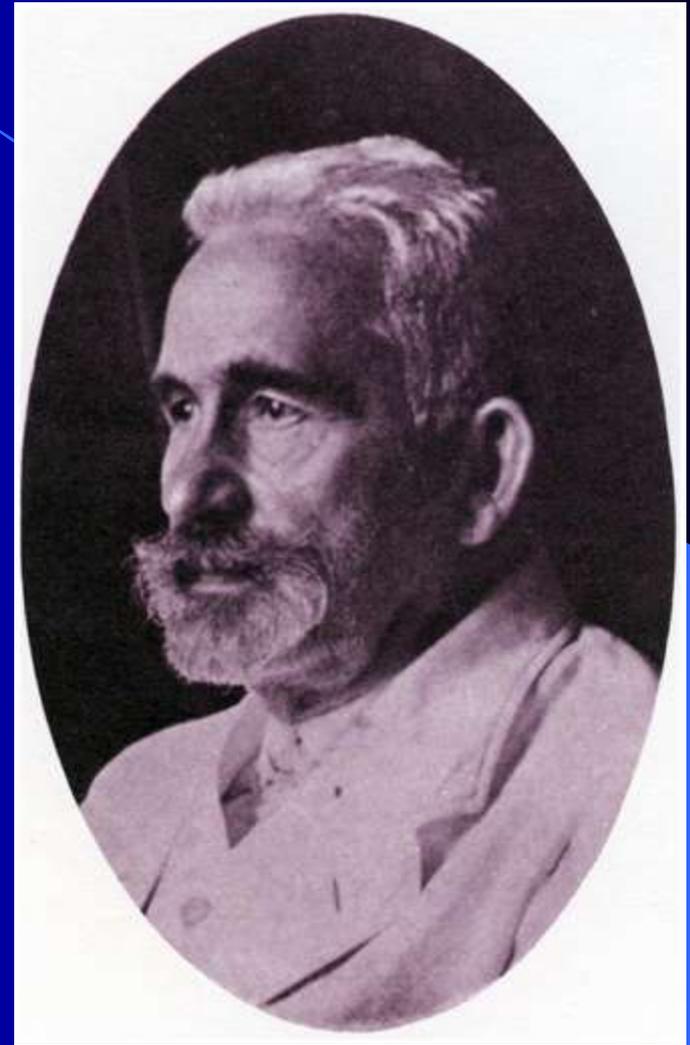
Historical evolution of the MDI construct and the unipolar-bipolar distinction

- Falret and Bailarger (1854)
- Griesinger (1867)
- Kahlbaum (1882)
- Kraepelin (1913)
- Kleist (1950)
- Circular insanity and insanity of double form
- Mania and melancholia emerging from a single disorder
- Cyclothymia as a group of circular disorders
- Manic-depressive insanity (includes recurrent melancholia)
- Bipolar vs. unipolar manic-depressive subtypes

Manic-Depressive Psychosis

“includes ... the whole domain of so-called periodic and circular insanity ... mania, **the greater part of melancholia** and ... amentia. Lastly we include here certain colorings of mood, some of them periodic, some of them continuously morbid ...

[which] pass over without sharp boundary into the domain of personal disposition.”

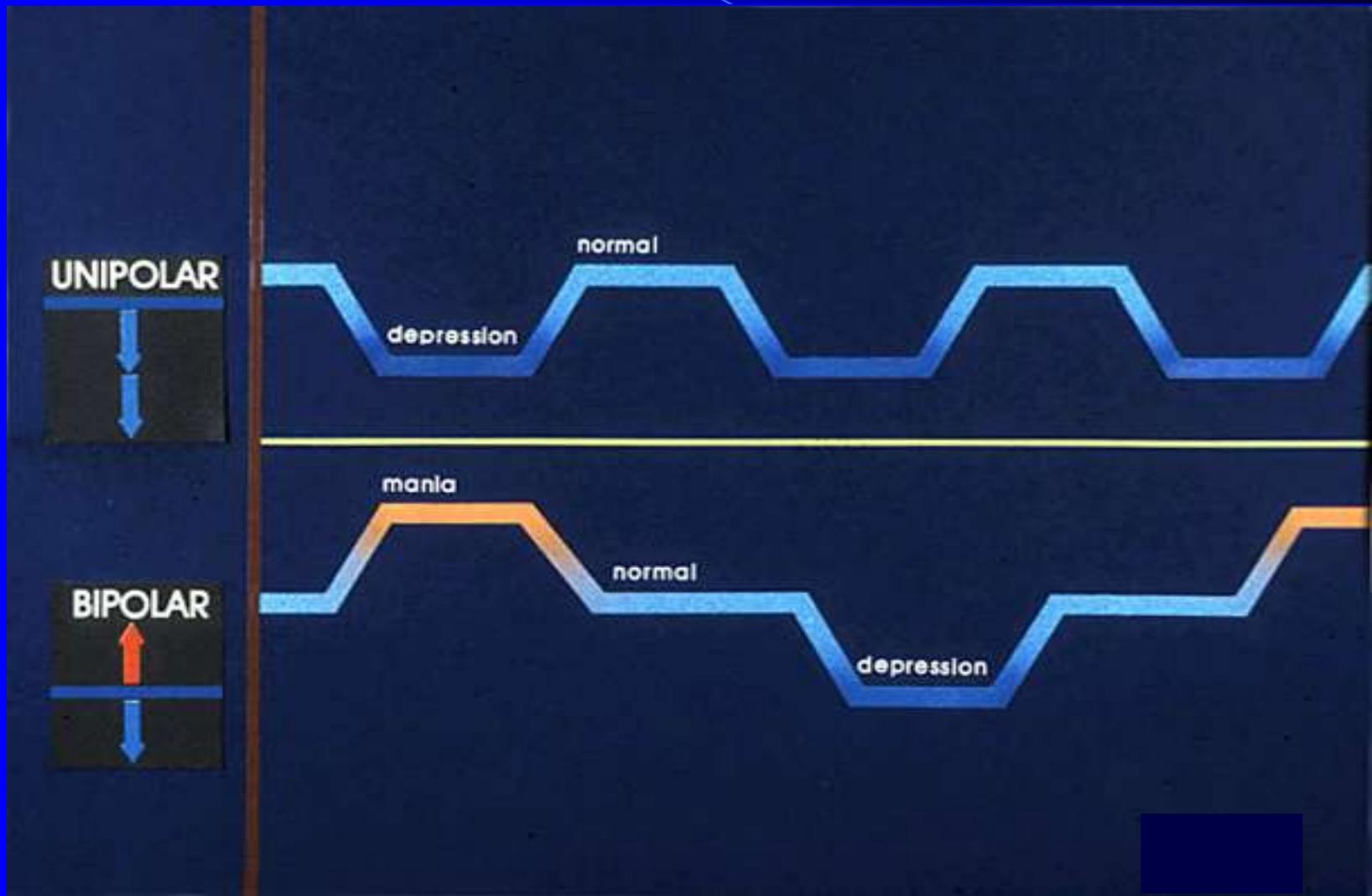


E. Kraepelin, 1899

Historical evolution of the MDI construct and the unipolar-bipolar distinction

- Leonhard (1957)
- Angst and Perris (1960's)
- Dunner Gershon and Goodwin (73)
- Akiskal (1980)
- Goodwin and Jamison (1990;2007)
- DSM IV (1994)
- Elaborated the polarity hypothesis
- Further elaborated the polarity concept
- Type II bipolar disorder (depression + hypomania)
- Broad “bipolar spectrum” concept
- Manic-Depressive Illness (BP & Recurrent Unipolar)
- Bipolar-II, cyclothymia, and rapid cycling included

Kraepelin's Manic-Depressive Illness

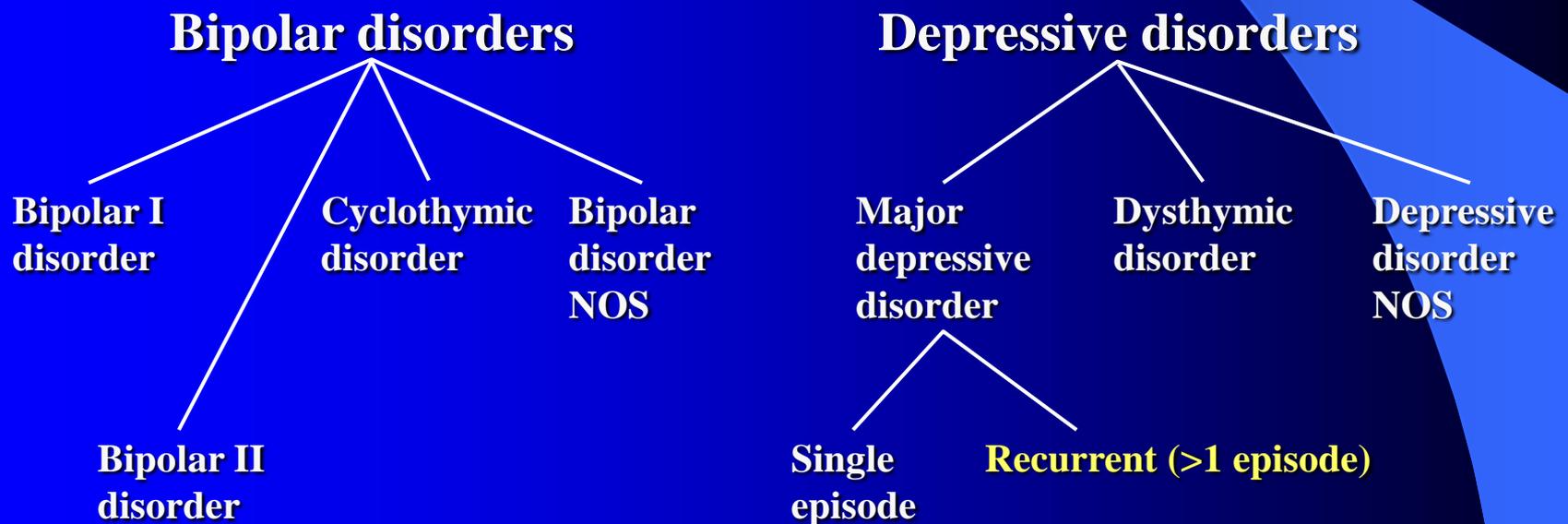


Kraepelin E. *Manic-Depressive Insanity and Paranoia*. Edinburgh, Scotland: Livingstone; 1921.

As originally formulated by Leonhard, and by Angst, Perris, Winokur, Goodwin and their colleagues, both unipolar and bipolar described patients with a phasic or cyclic course of recurrent episodes characterized by autonomous “endogenous” features.

DSM-5 Classification of Mood Disorders

Mood disorders



By separating out the Bipolar subtype from the top as a distinct illness, DSM 5 departs from Kraepelin and the originators of the UP – BP distinction by placing the primary emphasis on polarity at the expense of cyclicity or recurrence.

Highly Recurrent Unipolar Depression (Cyclic Depression)

- Bipolar family history
- Bipolar-like age of onset (teens and 20s)
- High episode frequency
- Manic/hypomanic switch with antidepressants
- Prophylaxis with lithium > imipramine
 - (Lithium is anti-cyclic, not just anti-bipolar)
- UNFORTUNATELY DSM-5 HAS NO SUCH CATEGORY

Why has polarity trumped cyclicality?

- Bipolarity can be determined on the basis of a single manic (or hypomanic) episode, and a UP diagnosis can be made with some confidence if age of onset is >35 or, if an earlier age of onset, after 2 - 3 depressions without a mania/hypomania.
- The quantification of Cyclicality (recurrence) requires long periods of observation, ideally prospectively. This is especially difficult to accomplish in countries with high population mobility, such as the United States.
- DSM 5 diagnoses are cross-sectional

Unintended consequences of polarity as the preeminent organizing principal for the affective disorders

- Under-diagnosis of Bipolar Disorder
- Biological and genetic research
- Treatment
 - Heterogeneity of UP samples
 - Treatment resistant UP depression
 - Dearth of prophylactic data on highly recurrent depression

Genetics

- Among 321 1st degree relatives of BP probands, more (32%) had a diagnosis of recurrent UP (avg of 7 prior episodes) than a diagnosis of BP I (23%)
- This same study provided evidence that recurrence was familial, and it was largely independent of polarity

Relative Risk for Bipolar Disorder in First-Degree Relatives of Patients with Major Mood Disorders

Bipolar (I & II)	10.7
All Major Depression	2.8
Early Onset Recurrent Depression subgroup	4.5

- Conflicting findings among studies of UP-BP differences in biological measures probably reflect the fact that the UP and BP samples are not matched for cyclicity (recurrence)
- Indeed, UP heterogeneity with respect to recurrence may explain many of the conflicting results in biological studies of UP depression

The extended Bipolar Spectrum of Akiskal

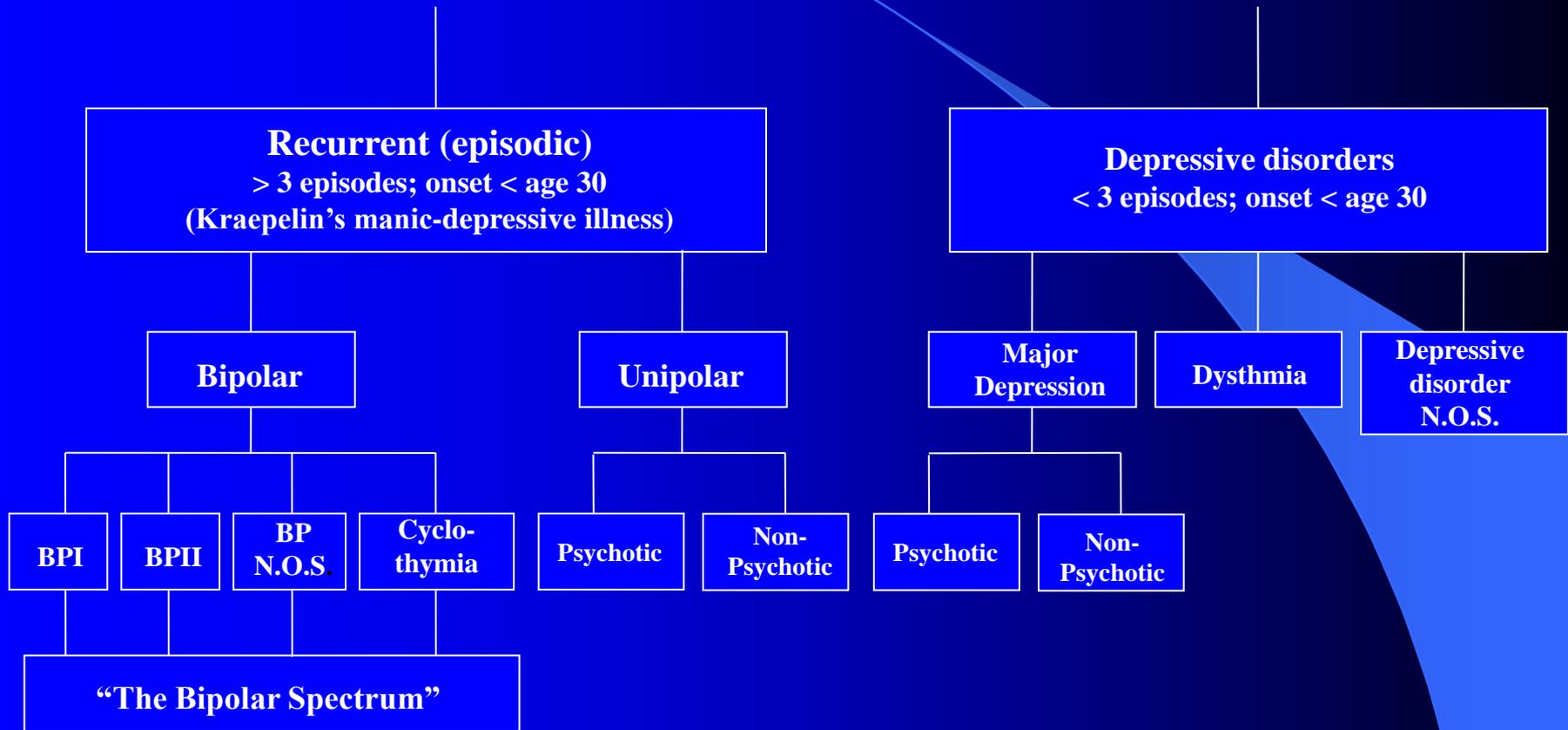
- **Recurrent unipolar is included in the bipolar spectrum (as “pseudo-unipolar”)**
 - **Although they are similar to bipolar patients in age of onset, family history, and frequency of recurrences, and some have a few symptoms analogous to mania or hypomania when depressed, as a group, highly recurrent unipolar patients are NOT bipolar.**

Manic-Depressive Spectrum or Bipolar Spectrum?

Clearly some patients with unipolar depression belong in the bipolar spectrum, but what about those **WITHOUT** “manic-like” symptoms while depressed?

A revised DSM, initially differentiating the more recurrent forms of affective disorder and **then** applying the UP-BP distinction would emphasize the close relationship between bipolar and highly recurrent unipolar depression without having to include all recurrent depression in the bipolar spectrum

Mood or Affective Disorders



Highly Recurrent Unipolar Depression (Cyclic Depression)

- Bipolar family history
- Bipolar-like age of onset (teens and 20s)
- High episode frequency -in the range of BP pts

Prophylaxis with lithium > imipramine
– (Lithium is anti-cyclic, not just anti-bipolar)

- DSM-5 HAS NO SUCH CATEGORY

Conceptual challenges to understanding maintenance treatment of Recurrent Unipolar Depression

- Distinguishing highly recurrent from DSM IV recurrent (> 1 episode)
- Distinguishing the continuation phase of treatment from the maintenance phase

Three Phases of Drug Treatment of Affective Disorders

Acute



Control of acute symptoms

Continuation



Maintain control of acute episode

Maintenance or prophylaxis,
ie, **mood stabilizer**



Prevent or attenuate new episodes

- In the major reviews of strategies for preventing relapse and recurrence in major depression (including the APA guidelines) most of the patients only meet the broad DSM definition of “recurrent” (>1 episode) and most of the emphasis (and data) is about **relapse** prevention.
- All of these reviews focus exclusively on antidepressants

- Given that the focus is on long term maintenance, why aren't mood stabilizers discussed in these reviews and guidelines?

I would suggest that, at least in part, this is so because our current diagnostic system implies that high rates of recurrence (and therefore the need for prophylaxis) is only associated with a bipolar diagnosis

- Consider Lithium for example

- In 1897 Carl Lange reported ten patients hospitalized for suicidal, recurrent “endogenous” depression; they were treated successfully with lithium (plus light therapy and exercise), but relapsed when lithium was stopped following discharge.
- Thus the first report of lithium as a therapeutic agent involved recurrent depression

Lithium Prophylaxis in Recurrent Unipolar Depression (Davis 99)

- A meta-analysis of 9 randomized placebo controlled studies (229 patients)
- Relapse rates: Placebo: 75% Lithium: 36% ($p < 0.000000001$)
- Most of the studies required 2-3 hospitalizations in the 2 years prior to randomization (i.e. highly recurrent)
- It is conceivable that, today, some of the UP patients might be considered as part of the BP spectrum.
- This represents more data on the prophylactic effect of lithium in recurrent unipolar depression than all putative mood stabilizers (other than lithium) in Bipolar Disorder

Lithium and Lithium vs AD's in Recurrent Unipolar Depression: A Meta-analysis of randomized studies (5-36 mo, mean 16)

10 studies, Lithium vs placebo:

7 studies were of patients with “frequent episodes” with cycle lengths of 12 to 24 months (Highly recurrent)

78% reduction in new episodes ($p < .00006$)

7 studies, Lithium vs Antidepressants:

30% fewer episodes on lithium (ns). This difference was larger and became significant when manic relapses were included

- What about maintenance antidepressants in Recurrent Unipolar Depression?

Relapse prevention with AD in depressive disorders: A systematic review (Geddes et al, 2003)

- Only 4 of the 37 trials (211 pts) involved recurrent UP (>1 episode) with 4-6 months of treatment before randomization (to get beyond continuation phase) and follow-up of 18-36 mo:
 - Relapse on AD: 15% vs Pb 38%
 - Risk reduction seemed independent of follow-up length
 - “within the trials there is not a clear distinction between the continuation and maintenance phase treatment effects”

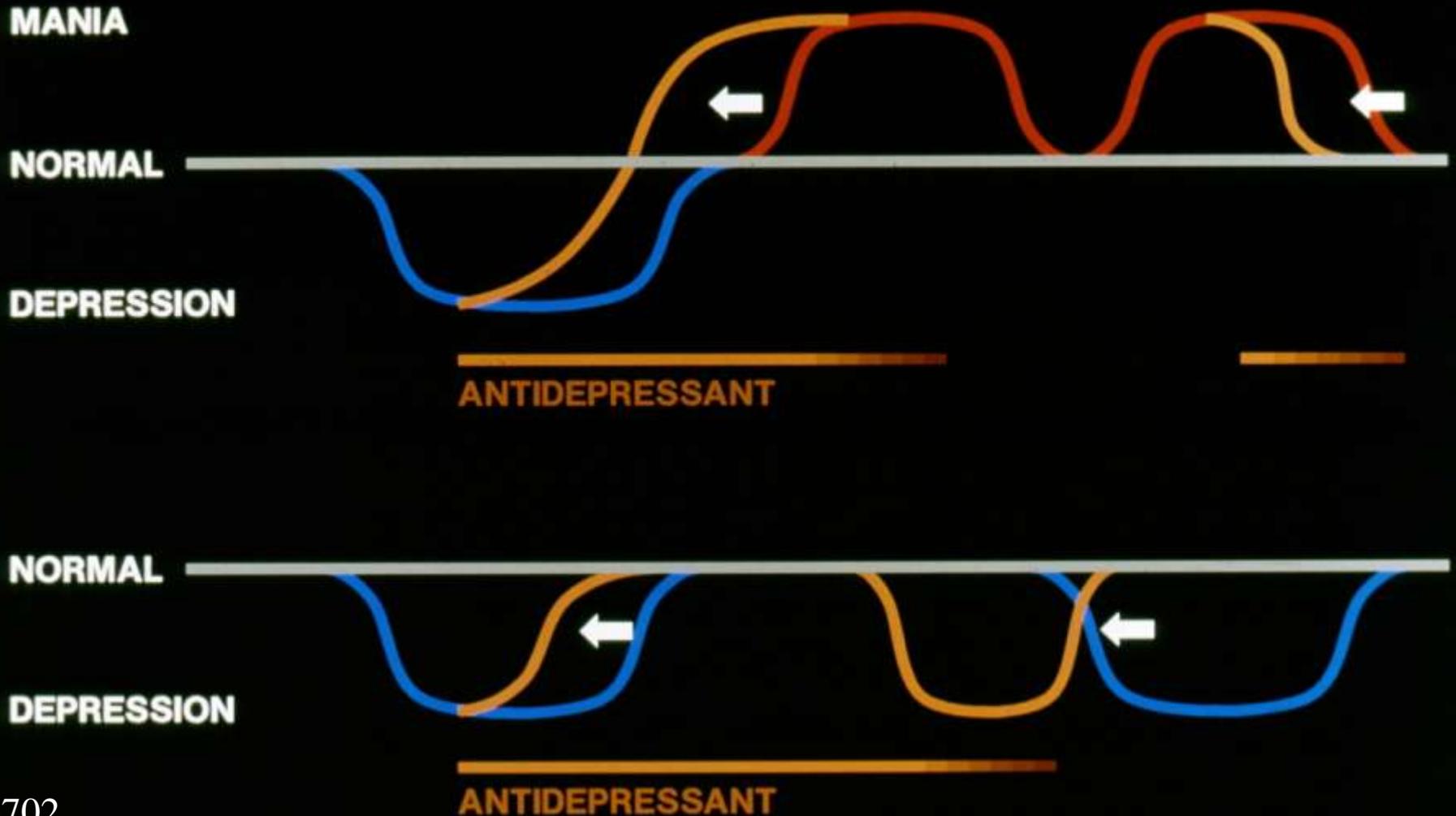
Tachyphylaxis (poop out) of antidepressants in Major Depressive Disorder

- An observational study (the NIMH collaborative) of 103 unipolar patients who were treated with and maintained on an antidepressant (171 intervals of maintenance Rx) for a median duration of 5 mo)
- Tachyphylaxis observed in 25% of the intervals (recurrence of symptoms after a minimum of 8 consecutive weeks with no or mild symptoms)
- Likelihood of tachyphylaxis did not correlate with the number of lifetime episodes, but only 31% had 3 or more previous episodes

Loss of Antidepressant Efficacy During Maintenance: A review of 11 Placebo controlled studies

- 8 trials involved tricyclics, 3 involved SSRI's
- Relapses in trials that continued the full acute dose in the maintenance phase: 9% to 33%
- Possible explanations given:
 - 1) Loss of placebo effect 2) Tolerance
 - 3) Pharmacokinetic changes 4) Increase in disease severity
 - 5) Change in disease due to the drug
 - 6) Prophylactic inefficacy 7) **Unrecognized cycling**

Antidepressants and Cycle acceleration



Treatment Resistant Depression: How much of it is recurrent depression?

- N=61
- TRD defined by failure to respond to two adequate trials of antidepressants
- Response defined as two months without symptoms or impairment
- 35% initially diagnosed with bipolar type I or type II
- 65% diagnosed unipolar Major Depression

Treatment Resistant Depression

- On re-evaluation, 59% were diagnosable with bipolar disorder type I (3%), II (43%) or NOS (13%).
- Of the 41% still diagnosable with unipolar MDD, 52% were diagnosable with “BP spectrum” disorder (primarily recurrent UP with a BP FH, [which I consider not properly in the BP spectrum])
- Thus 79% of an initially treatment resistant sample had a “bipolar spectrum” condition which included recurrent unipolar with a bipolar FH

Observational TRD treatment

- Entire sample n=61
- At intake:
 - 93% treated with antidepressants
- At 1 year follow-up:
 - 52% of those on antidepressants were taken off
 - 66% received new treatment with mood stabilizers or atypicals (**including recurrent unipolar** patients)
- CGI response at 1 year from 4 to 2: From moderate illness to minimal illness
- Best level of evidence to date on this topic, though not randomized

Maintenance Treatment of Recurrent Depression

- What is the evidence that mood stabilizers other than lithium may have a role in the maintenance treatment of recurrent unipolar depression?
- Especially, what about lamotrigine ? (Given that it tended to be superior to lithium in the prevention of depressive episodes in bipolar disorder)
- And what about quetiapine ? (FDA indicated for acute treatment of BP depression, and effective as an adjunct for long term prevention of BP depression)

- Surprisingly there are no published controlled maintenance studies of lamotrigine or of quetiapine (or any atypical) in recurrent unipolar depression

The Treatment of Recurrent Brief Depression

- There are a small number of RTC's evaluating SSRI's, with conflicting results, but more recent studies are positive.
- There are several positive case reports involve lithium, carbamazepine and lamotrigine

Conclusions

- Our current diagnostic system leaves the unipolar category so broadly defined (i.e. not bipolar) as to be almost meaningless; this heterogeneity confounds genetic, biological and psychological studies, and most importantly, studies of drug efficacy, both acute or maintenance.
- Thus, while highly recurrent unipolar patients represent one third of all major depression, they have not been the focus of any industry trials (eg: lamotrigine story)
- By obscuring the relationship between bipolar disorder and highly recurrent unipolar depression, DSM IV contributes to the underdiagnosis of bipolar disorder which is associated with inappropriate treatment for some depressed patients