Gender and Mood

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Mood Disorders with Sexual Dimorphism

- Unipolar depression (MDD): females > males
- Bipolar disorder: females more prone to rapid cycling
- Mood syndromes related to hormonal shifts:
  - Premenstrual dysphoric disorder (PMDD)
  - Postpartum depression
  - Perimenopausal and postmenopausal depression

Unipolar Illness in Women: *Incidence and Prevalence Data*

National Comorbidity Survey (NCS):
- **MDD: 21% ♀ / 12.7%♂**

PMDD 5%

Post-partum affective illness:
- "Blues" 26-85%; up to 10 days postpartum
- Depression 10%; onset within first 4 wks postpartum
- Psychosis 0.5%; highly recurrent

Perimenopausal age range:
- 10% incidence of MDE symptoms
- ↑ ratio of MDE (♀:♂) 4:1

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Premenstrual Dysphoric Disorder

A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):

(1) markedly **depressed mood**, hopelessness or self-deprecating thoughts
(2) marked **anxiety**, tension, feelings of being "keyed up," or "on edge"
(3) marked **affective lability**
(4) persistent and marked **anger or irritability** or increased interpersonal conflicts
(5) **decreased interest** in usual activities (e.g., work, school, friends, hobbies)
(6) subjective sense of **difficulty in concentrating**
(7) **lethargy**, easy fatigability, or marked lack of energy
(8) marked **change in appetite**, overeating, or specific food cravings
(9) **hypersomnia or insomnia**
(10) a subjective sense of being **overwhelmed or out of control**
(11) **physical symptoms**: e.g., breast tenderness, headaches, joint pain and "bloating."

Premenstrual Dysphoric Disorder

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as Major Depressive Disorder, Panic Disorder, Dysthymic Disorder, or a Personality Disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

DSM-IV Criteria Sets for Further Study, 1994

Treatment of PMDD

- Serotonin Specific Reuptake Inhibitors (SSRIs)
- Luteal phase treatment with SSRIs
- Gonadal steroids
- GnRH agonists (e.g., Lupron)

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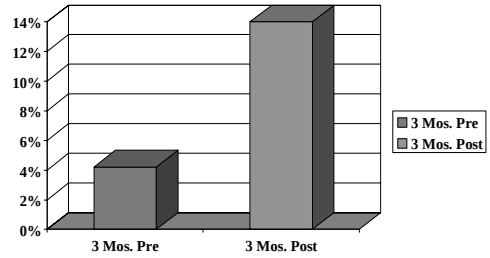
Post-partum Depression (PPD)



Kumar and Robson, 1984

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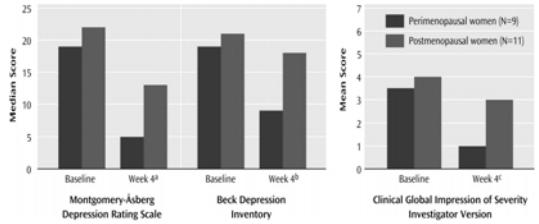


Gender Effects in BPD

- Men and women with BPD have:
  - Equal prevalence rates.
  - Similar age of onset.
- Men and women with BPD differ in terms of longitudinal course:
  - Rapid Cycling Bipolar Disorder (RCBD).
  - Hormonal transitions.

Rapid Cycling Bipolar Disorder

- Derived from studies of lithium failure
- Definition: 4 or more episodes, last 12 months
- Prevalence = 15% of BPD patients
- Not a stable phenotype
- Predictors:
  - female gender
  - antidepressant use
  - thyroid disease

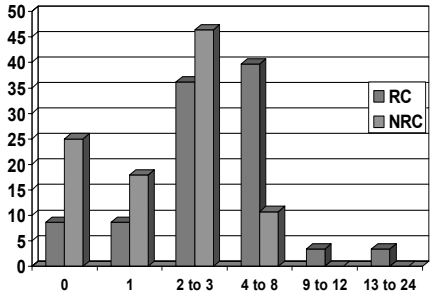
Dunner and Fieve, 1974. Dunner 1979; Winokur 1969

Validation of Rapid Cycling for DSM-IV

- Pooled data from four academic sites.
- All sites actively studying RC (to improve reliability/accuracy of assessment of episode number).
- Comparison of subjects with and without lifetime history of RC (n=120).
- Episodes distinct if polarity switch occurred or remission > duration of proximate episode.

Bauer et al, 1994

Episodes During 12 Months Follow Up



Bauer, et al, 1994

Gender and Episode Frequency

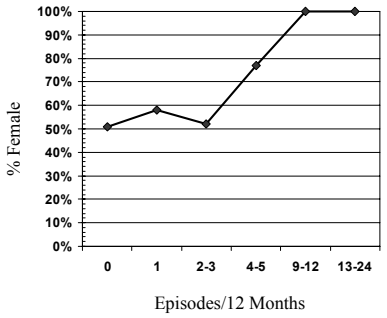


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TABLE 1. Rapid Cycling in Women and Men With Bipolar Disorders in 10 Studies

Study	Year	Number of Subjects	Women N	Women %	Men N	Men %	Rapid-Cycling Patients[a] Total N	Total %	Women N	Women %	Men N	Men %	Risk of Rapid Cycling[b] Ratio (W/M)	χ^2 (df=9)	p
Dunner et al. (1)[c]	1977	306	151	49.3	155	50.7	40	13.1	28	18.5	12	7.7	2.39	7.85	0.009
Kukopulos et al. (2)[d]	1980	434	256	59.0	178	41.0	87	20.0	61	23.8	26	14.6	1.63	5.57	0.03
Cowdry et al. (14)[e]	1983	43	30	69.8	13	30.2	24	55.8	20	66.7	4	30.8	2.17	3.40	0.07
Joffe et al. (15)[e]	1988	42	27	64.3	15	35.7	17	40.5	7	25.9	10	66.7	0.39	5.06	0.02
Nurnberger et al. (16)[e]	1988	195	113	57.9	82	42.1	29	14.9	25	22.1	4	4.9	4.53	9.84	0.002
Coryell et al. (3)[e]	1992	243	130	53.5	113	46.5	45	18.5	32	24.6	13	11.5	2.14	6.89	0.01
Lish et al. (17)[f]	1993	89	65	73.0	24	27.0	45	50.6	37	56.9	8	33.3	1.71	3.02	0.08
Bauer et al. (4)[g]	1994	239	144	60.3	95	39.7	120	50.2	84	58.3	36	37.9	1.56	9.56	0.003
Maj et al. (5)[g]	1994	111	62	55.9	49	44.1	37	33.3	24	38.7	13	26.5	1.46	1.83	0.25
Current study[g]	1998	355	227	63.9	128	36.1	54	15.2	39	17.2	15	11.7	1.47	1.89	0.22
Total		2,057	1,205	58.6	852	41.4	498	24.2	357	29.6	141	16.5	1.79	59.5	<0.0001

[a] Four or more episodes per year.
[b] Mantel-Haenszel pooled contingency analysis.
[c] Feighner criteria.
[d] ICD-9 criteria.
[e] Research Diagnostic Criteria.
[f] DSM-III-R criteria.
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Tondo and Baldessarini, *Am J Psychiatry*,1998

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Rapid Cycling in Women: Theories

- Increased depressive episodes in women with BPD leading to increased anti-depressant use.
- Hormonal fluctuations acting to drive episode frequency.

Episode Type by Gender

- 2 retrospective studies suggest more hospitalizations for mania in men and depression in women.
  - Angst, 1978.
  - Roy-Byrne, 1985.
- 2 studies found no gender difference.
  - Winokur et al, 1994. 10 year prospective study, n=131.
  - Hendrick et al, 2000. Retrospective study, n=131.

Are Women More Vulnerable to AD?

- Retrospective review of 129 patients (55% female)
- Rate of rapid cycling:
  - 56% of pts with prior AD exposure vs. 42% without
  - Females: 77 vs. 41%
  - Males: 36 vs. 42%

Yildiz and Sachs, 2003

Evidence for Hormonal Effects on Mood in Affective Illness

1. Unipolar syndromes occur during drops in estrogen/progesterone:
   - Premenstrual
   - Postpartum
   - Perimenopausal
2. Iatrogenic affective symptoms:
   - HRT lowers depression scores.
   - Affective symptoms have been associated with OCP and GnRH agonists.

What do we know about bipolar disorder during times of hormonal flux?

Estimated 7% of women in asylums had symptoms originating in post-partum period.

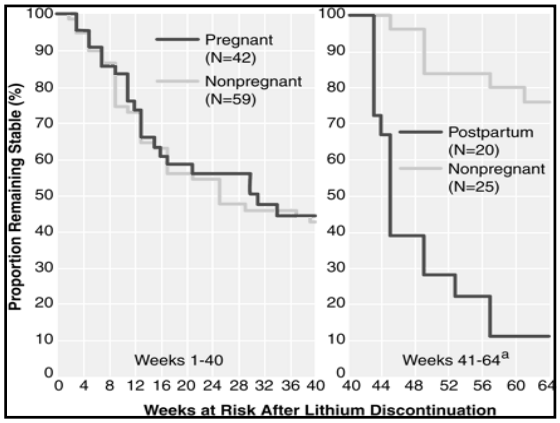
Focus on psychosis, catatonia and delerium.

"Where mania really appears in the puerperal state, it is… only a link in the chain of attacks of maniacal-depressive insanity. The puerperium cannot therefore be regarded as the cause, but only as the last impulse to the outbreak of the disease"

E. Kraepelin, 1913

Postpartum Vulnerability

- NIMH Genetics Initiative (1998):
  - ½ bipolar women report "severe emotional disturbance" related to childbirth.
  - 1/3 of these began during pregnancy.
- Viguera, et al (2000):
  - Retrospective study of women with bipolar I/II discontinued from lithium.



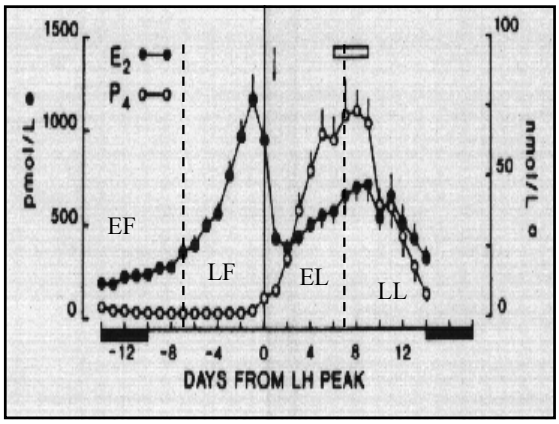
Working hypothesis: Rapid cycling is more common in women due to triggering by hormonal cycles.

- Mood should fluctuate in relation to the menstrual cycle in women with RCBD.
- Episodes may preferentially originate in particular phases of menstrual cycle.

Perimenstrual Mood Changes

- 25 female RCBD subjects
- Daily self-ratings of mood for mean of 12 menstrual cycles
- Found no *systematic* relationship between mood and cycle but 11/25 had consistent changes.
- Limitation in mood instrument.

Leibenluft et al 1999



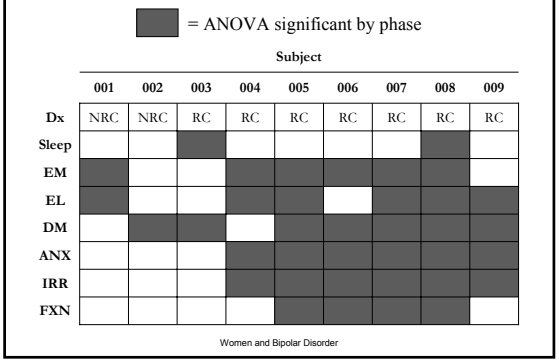
Method

- All rated days were allocated to one of the four phases: EF, LF, EL or LL based upon timing of menses.
- Mean and SD of each phase obtained for each subject and converted to z scores.
- Comparisons made within subject across the cycle and within the entire group.

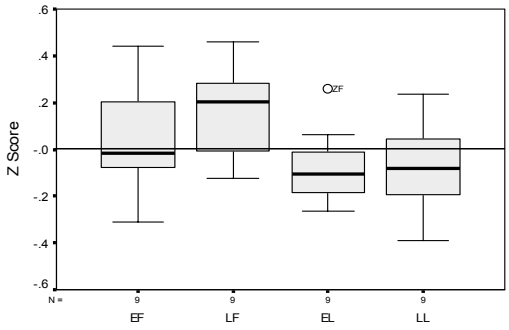
Subjects

ID	Type	Cycles Studied	Mood Stabilizers
001	NRC	22	VPA
002	NRC	13	LTG
003	RC	9	VPA, LTG
004	RC	19	Lithium, VPA, LTG
005	RC	9	LTG
006	RC	11	LTG, quetiapine, TPM
007	RC	7	Lithium
008	RC	10	Lithium
009	RC	5	Lithium, VPA, LTG, ziprasidone
	Mean	11.7	

Menstrual Phase Effects



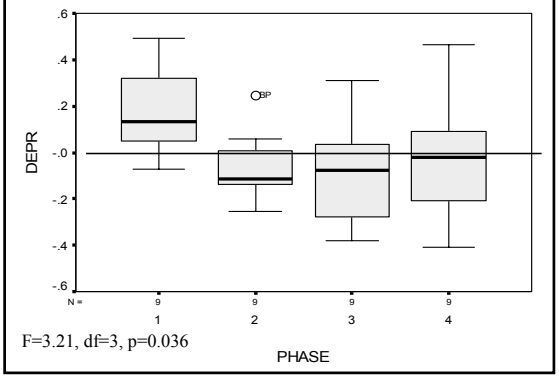
Elevated Mood Z Scores



F=2.90, df=3, p=0.05

Menstrual Cycle Phase

Depressed Mood Z Scores

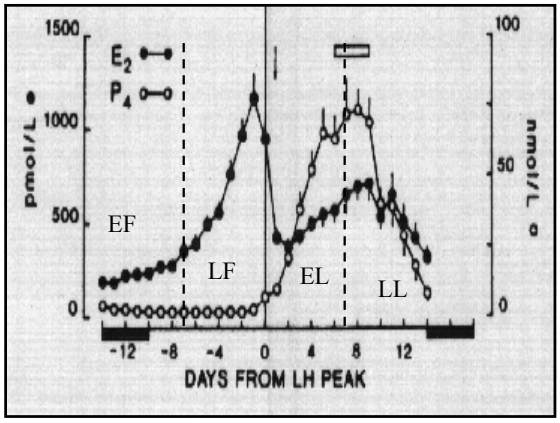


F=3.21, df=3, p=0.036

PHASE

Preliminary Observations

- All subjects had at least one dimension of mood which varied significantly with menstrual phase.
- There were differences between individuals in phase relationships (Subgroups?).
- As a group, elevated mood peaked in the late follicular phase and depressed mood in early follicular phase.



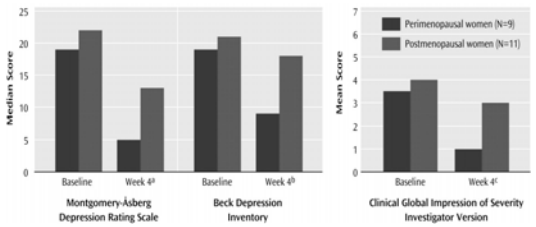
Perimenstrual Mood Changes
Possible Pathophysiology

	Estrogen	Progesterone	Mood
Early Follicular	↔	↔	**Depressed**
Late Follicular	↑	↔	**Elevated**
Early Luteal	↘↗	↑	**Stable**
Late Luteal	↓	↓	

- Is estrogen an antidepressant?
  - Clinical trials
  - Neurotransmitter effects: 5HT
- Is progesterone a mood stabilizer?
  - Neurosteroids
  - Neurotransmitter effects: glutamate, GABA

Is Estrogen an Antidepressant?

- Potential mechanism: 5HT modulation
- Clinical data:
  - Werner et al 1934: estrogen injection > placebo for depression.
  - Improvement in depressive symptoms in postmenopausal women without MDD.
  - Variable results across several studies of estrogen in perimenopausal/postmenopausal women with MDD.

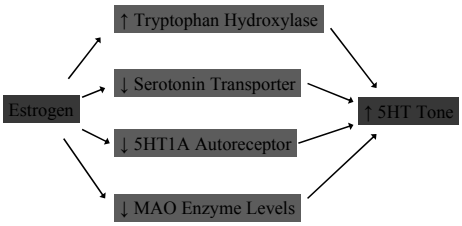


Estrogen in Peri-Menopause

- N=50 in perimenopause
- MDD, dysthymia or minor depression
- Not receiving psychotropics
- Double blind, placebo controlled treatment with 100 μg transdermal 17β-estradiol.

Soares et al 2001

Estrogen Effects on 5HT

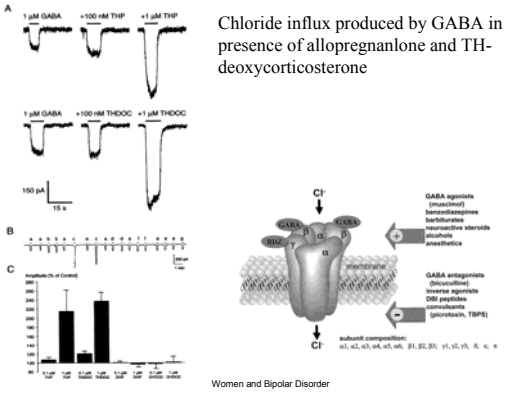


Evidence for a 5HT/Estrogen Connection

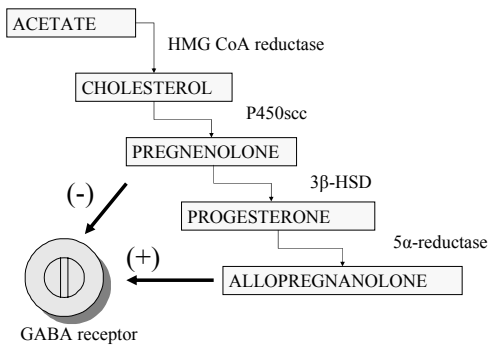
- PMDD responding to luteal SSRI use
- SSRI>TCA in postpartum depression:
  - PPD less response to TCA than non post-partum depression.
  - Open label response rates: 67% TCA, 79% SSRI.
  - 8 week open label sertraline: 95% response rate, 66% remission.
- Women may be more sensitive to tryptophan depletion

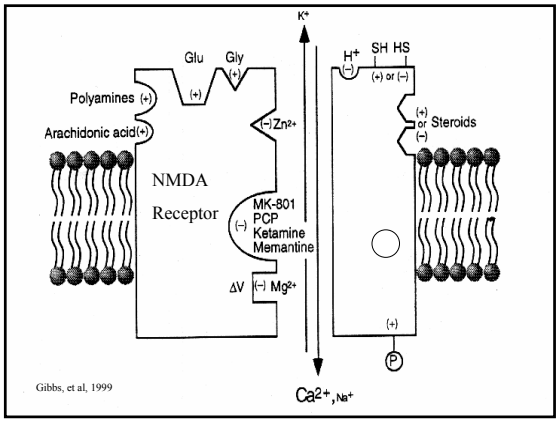
3α Reduced Neurosteroids

- Progesterone metabolites :
  - Allopregnanolone (3α, 5α TH Progesterone)
  - 3α, 5α TH deoxycorticosterone
  - Pregnanolone (3α, 5β TH Progesterone)
- Allosteric regulation: At nM concentrations, increase frequency and duration of GABA-induced channel opening. Most potent known endogenous positive allosteric regulator of $GABA_A$
- Direct agonism: At μM concentrations, produce Chloride influx without GABA



Chloride influx produced by GABA in presence of allopregnanlone and TH-deoxycorticosterone





Neurosteroid Effects

	GABA	Glutamate
Estradiol	-	-/+*
Pregnenolone-S	-	+
Progesterone	+	0
Pregnanolone –S	0	-
Allopregnanolone	+	0
Allopregnanolone-S	0	-

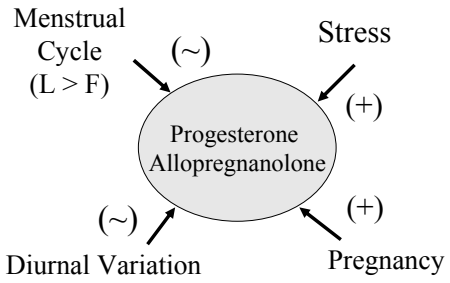
*NMDA(-) AMPA/Kainate (+)

Effects of Neurosteroids

- Antidepressant
- Anxiolytic
- Anticonvulsant
- Neuroprotective / neurotrophic

Mood Stabilizer Effects on GABA and Glutamate

	Glutamate	GABA
Lithium	↓	
Valproate	↓	↑
Carbamzepine	↓	
Lamotrigine	↓	
Topiramate	↓	↑



Treatment

"I don't mind at all. I take St. John's wort."

"I considered hormone replacement therapy. But for me, husband replacement therapy worked much better."

Conclusions

- Mood disorders are influenced by gender, likely via hormonal state and transitions. This allows for some degree of *anticipation*.
- Mood disorders are greatly under-treated; presenting an opportunity for internists, gynecologists and others to improve identification and reduce morbidity and mortality.
- The marriage of improved basic science knowledge of hormonal influences on brain and mood, as well as greater understanding of mood disorder phenomenology, provides hope for more specific and effective treatments.