Pharmacotherapy of Borderline Personality Disorder

Presented by: Michael Gitlin, MD
Distinguished Professor of Clinical Psychiatry,
Geffen School of Medicine at UCLA
Director, Adult Division of Psychiatry
Director, Mood Disorders Clinic

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Disclosures

In compliance with the ACCME Standards for Commercial Support of CME, I do not have any relevant financial relationships to disclose in relation to this presentation.

Educational Objectives

As a result of participating in this activity, you should be able to:

- Describe the difficulties in doing clinical research on medications in personality disorders
- Review the data supporting the use of medications in treating personality disorders
- Discuss the models that explain the use of medications in treating personality disorders

Methodological Problems in the PharmacoRx of Pers Disorders I

- Presence of multiple simultaneous PDs
  - Categorical vs. dimensional schemes
    - » Cutoff scores?
    - » One vs. zero sx (Zimmerman et al, 2012) associated with suicide attempts, decreased function and hospitalizations
- Comorbid Axis I disorders
  - Mean=3.4 disorders in CLPS study-McGlashan et al, 2000)
  - Comorbid anxiety, mood disorders and substance abuse all between 78-85% (Bohus et al, 2021)
- State/trait problems (within borderline pts)
- Short term vs. long-term studies

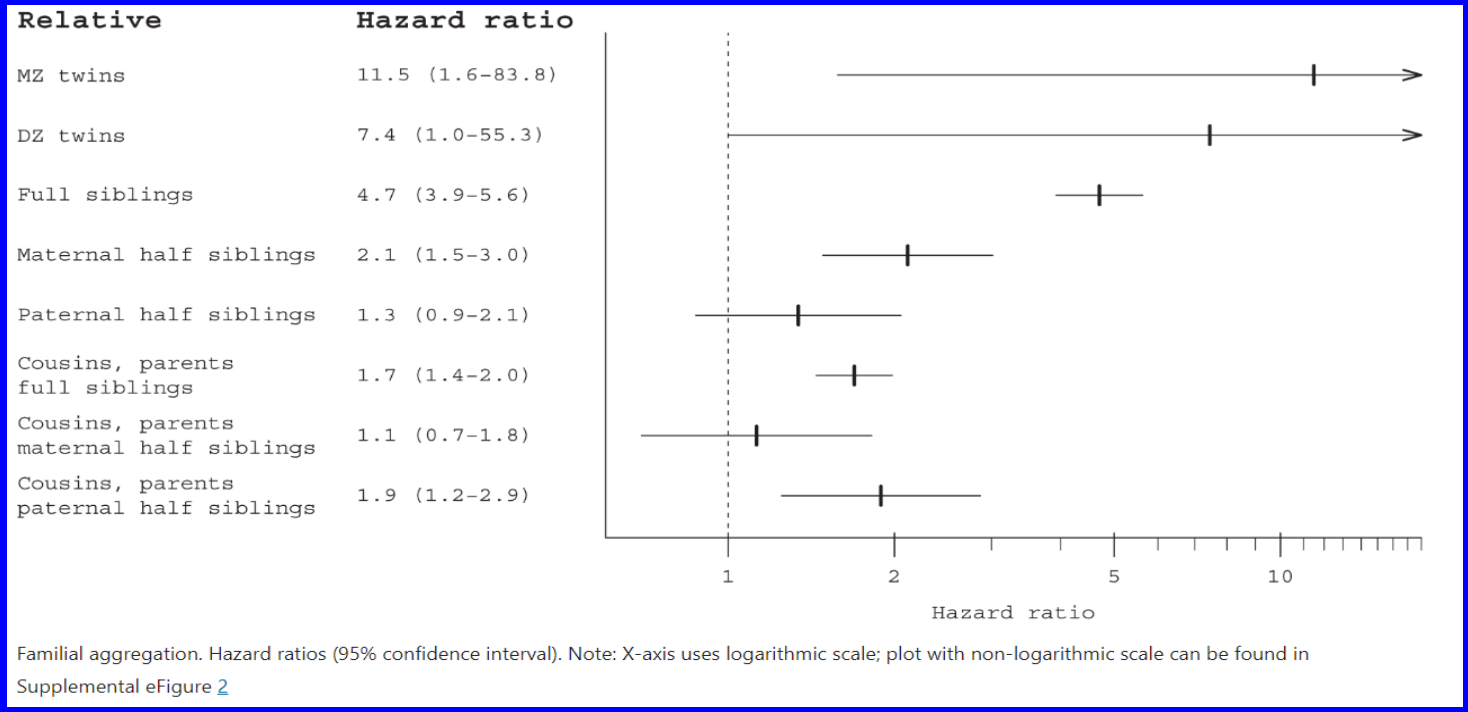
Methodological Problems in the PharmacoRx of Pers Disorders II

- Different inclusion criteria in studies
- Possible subtypes within a disorder (borderline PD)
- Forensic issues

Personality=

- Temperament
  - Consider core dimensions
- Learned behavior
- Yet, two dimensions related
  - Effect of early trauma/abuse
- Do meds target temperamental components of personality?
  - Heritability of PDs similar to Axis I disorders (0.5-0.7- Torgersen et al, 2000)
  - Kendler et al, 2008: 0.2-0.41
    - » Genetic factors for antisocial/borderline, and avoidant/schizoid

Familial Risk and Heritability of Diagnosed Borderline Personality Disorder: a Register Study of the Swedish Population



Familial aggregation. Hazard ratios (95% confidence interval). Note: X-axis uses logarithmic scale; plot with non-logarithmic scale can be found in Supplemental eFigure 2

Skoglund et al, 2021

Conceptual Models of PharmacoRx of Pers Disorders

- Treating the disorder itself
- Treating specific symptom clusters (behavioral dimensions)
  - Treating acute/behavioral sx
- Treating associated Axis I disorders
  - Comorbidity the rule, not the exception
  - Weak data on treating comorbid disorders in BPD (Ribeiro et al, 2025)

Symptom Clusters/Dimensions (Siever and Davis, 1990)

- Cognitive perceptual organization
- Impulsivity/aggression
- Mood instability
- Anxiety/inhibition

Familiality of Borderline Personality Disorder

- (Gunderson et al, 2011) Risk ratio=3.9
  - Seen with all four components of disorder (affective, interpersonal, behavioral and cognitive)
    - » Implying one unitary construct (Reichborn-Kjennerud et al, 2013)
- Heritability estimates-37-69%
- In study of twin pairs, both genetics and family environment make independent contributions (Belsky et al, 2012)

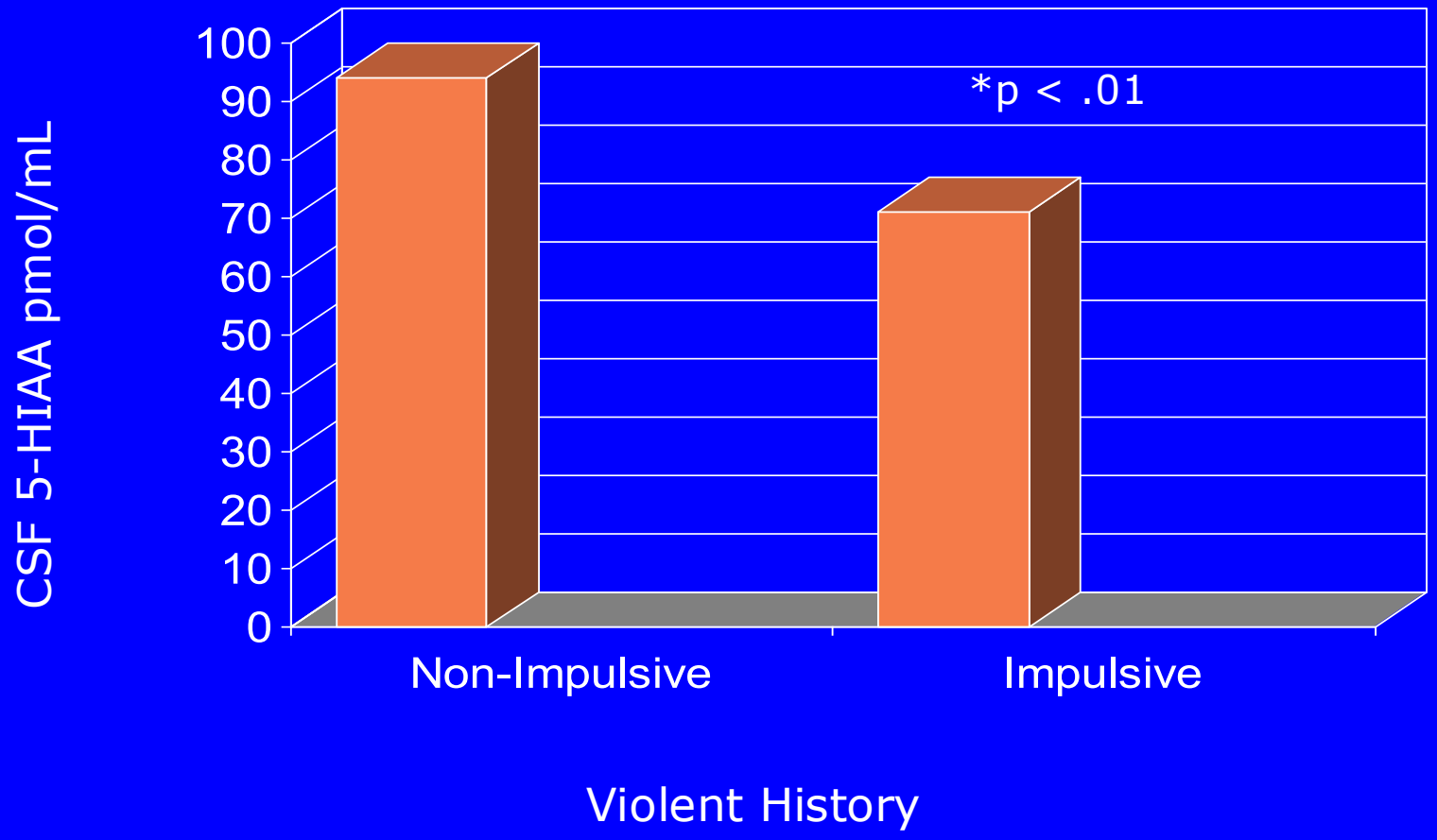
Cluster B Personality Disorders: PharmacoRxic Strategies I

- Impulsive/aggressive and mood instability dimensions
  - When comorbid with MDD, improvement in BPD sx precede MDD improvement, not vice versa (Gunderson et al, 2004)
  - Mood instability-between anger/anxiety/depression, NOT elation/depression (w/o BP II) (Koenigsberg et al, 2002)
  - Genetic contribution for impulsive traits

Antisocial Personality Disorder

- No studies examining pharmacoRxic approaches
  - ?Treat impulsive/aggressive subgroup
  - Distinguish between impulsive aggression and premeditated aggression

CSF 5-HIAA: History of Impulsive vs Non-Impulsive Violence in Violent Offenders



Linnoila et al 1983

Borderline Personality Disorder: PharmacoRxic Approaches I

- Common disorder- 2.7% (in Tomko et al 2014) to 6% in epidemiological study (Grant et al, 2008)
- 85% of all studies in the area
- Most medication classes evaluated
  - Antipsychotics
  - Antidepressants (SSRIs +MAOIs)
  - Mood stabilizers (Anticonvulsants +?lithium)
  - Others: OFC, omega 3 FA, naltrexone etc

Central Paradox of Pharmacotherapy of BPD I

- Virtually all reviews, meta-analyses and Practice Guidelines recommend very infrequent use of pharmacotherapy
  - See JAMA review -Leichsenring et al, 2023
    - » "Psychoactive medications do not improve the primary outcome of BPD"
  - And Lancet review-Bohus et al, 2021
    - » "Medications cannot be recommended for the treatment of BPD", and "Do not combine several drugs"

Central Paradox of Pharmacotherapy of BPD II

- Yet, studies of clinical practice indicate very, very common use of meds
- E.g. (Zanarini et al, 2004) Followup of 362 hospitalized pts with personality disorders, 1992-1995; 80% BPD
  - Four or more concurrent meds at 4/6 yrs
    - » Borderline-22%, 20%
  - At 6 yrs, 12% of borderline pts on 5 or more meds
- E.g. German inpatients with BPD in 2012 averaged 2 medications per pt on admission (Timaus et al, 2019)

Earlier Meta-Analyses of RCTs with Borderline PD

- N=27 studies with antipsychotics, antidepressants (including omega 3 FA), anticonvulsants
  - Included FGA studies
- Characteristics
  - Mean length= 12 wks (range=4-24 wks)
  - 80+%, all recent studies with outpatients
  - 50% with BPD; 50% with BPD + other PDs
  - All small n studies- only two studies>60 subjects; two>100 (OLZ, sponsored by Lilly)
  - Substantial dropout rates

Ingenhoven et al, 2010: Lieb et al, 2010

Meta-Analyses of Placebo-Controlled Studies of Medications in Personality Disorders

	Antipsychotics		Antidepressants		Mood Stabilizers		
Outcome Domain	Patients, n[b]	Effect Size[c]	Patients, n[b]	Effect Size[c]	No. of Studies[a]	Patients, n[b]	Effect Size[c]
Cognitive-perceptual symptoms	224	0.56*	139	0.11	2	74	0.42
Impulsive-behavioral dyscontrol	261	0.26	205	0.10	6	172	1.51**
Affective dysregulation							
Depressed mood	249	0.46	205	0.29	5	148	0.55**
Anxiety	226	0.23	193	0.30*	3	102	0.80***
Anger	201	0.69*	171	0.34*	7	230	1.33**
Mood lability	40	…	38	…	0	0	…
Global functioning	249	0.37**	153	0.22	3	102	0.79***

*P≤.05.

**P≤.01.

***P≤.001.

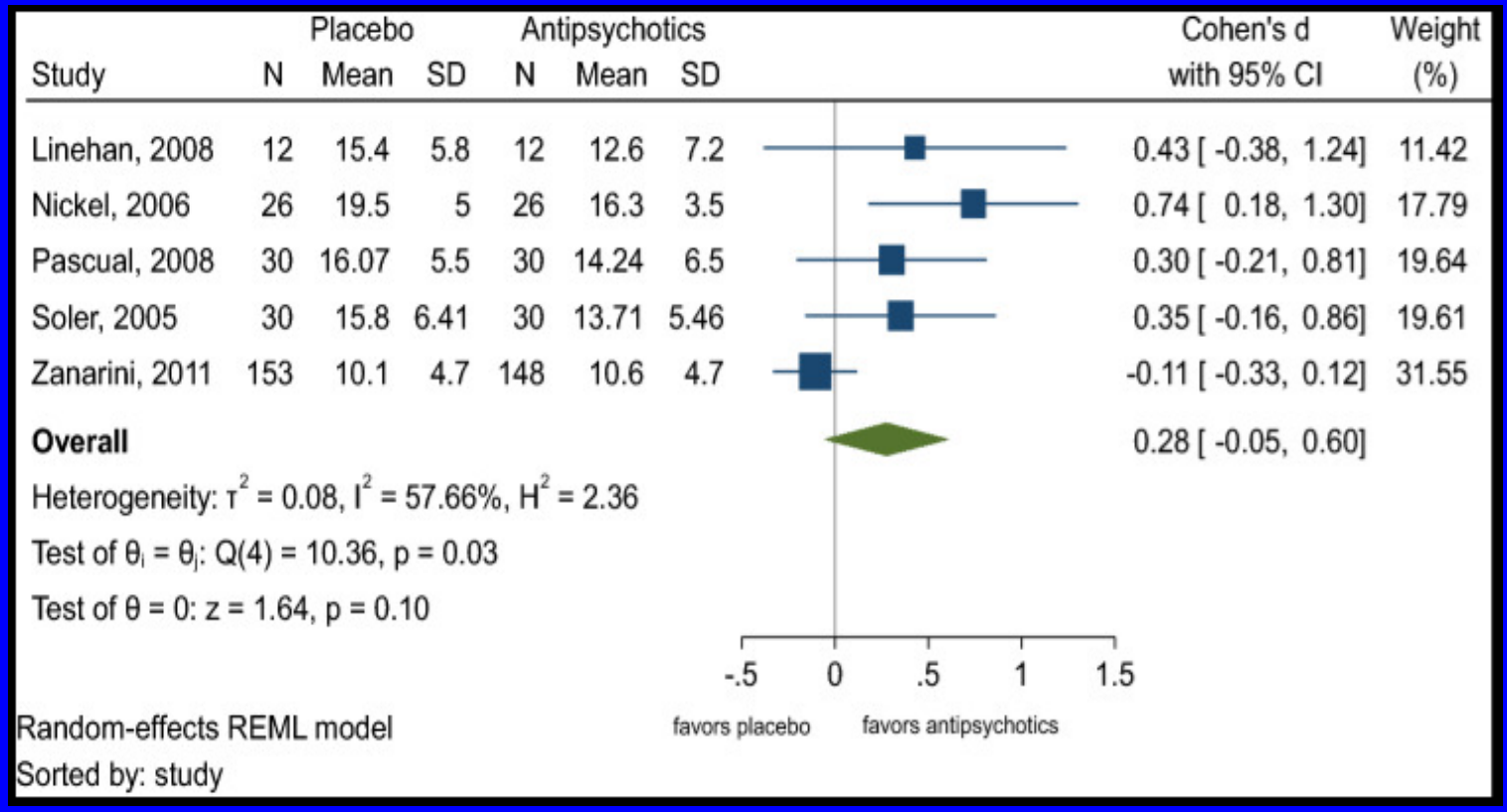
Symbol:…=meta-analysis did not apply

Ingenhoven et al, 2010

Borderline Personality Disorder: Antipsychotics I

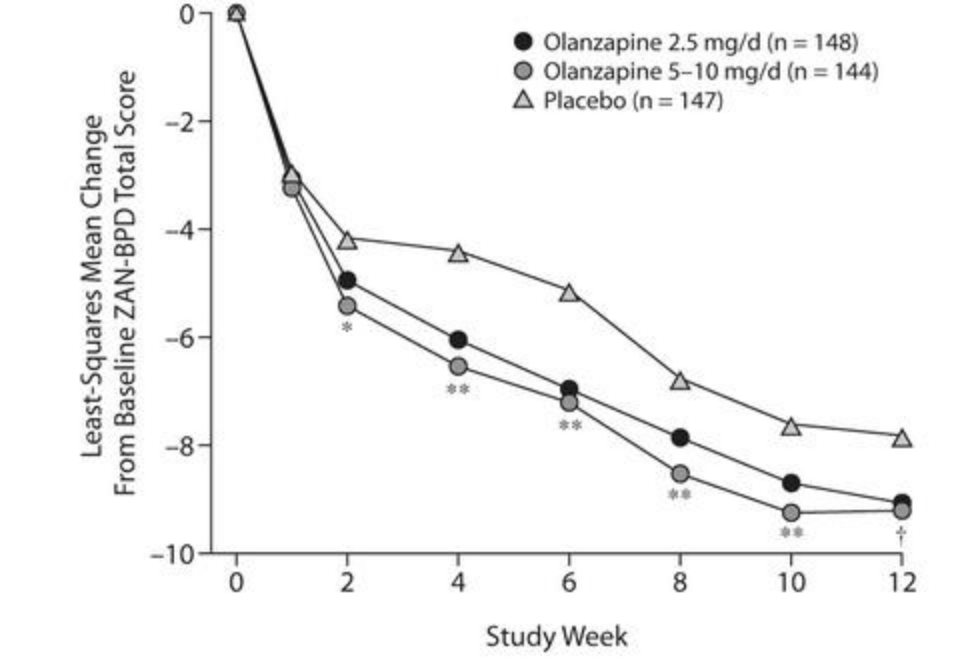
- FGAs-early studies, many agents +
  - Later studies show less consistent effect
  - Adherence problems
- Clozapine
  - Three open studies, evaluating patients with comorbid psychosis NOS, other severe Axis I disorders
  - Improvement seen in all studies
  - More recent RCT with poor recruitment (n=29, not 222) in inpt, severe BPD (Crawford et al, 2022)

SGAs for Borderline Personality Disorder (excluding FGAs)



Gartlehner et al, 2021

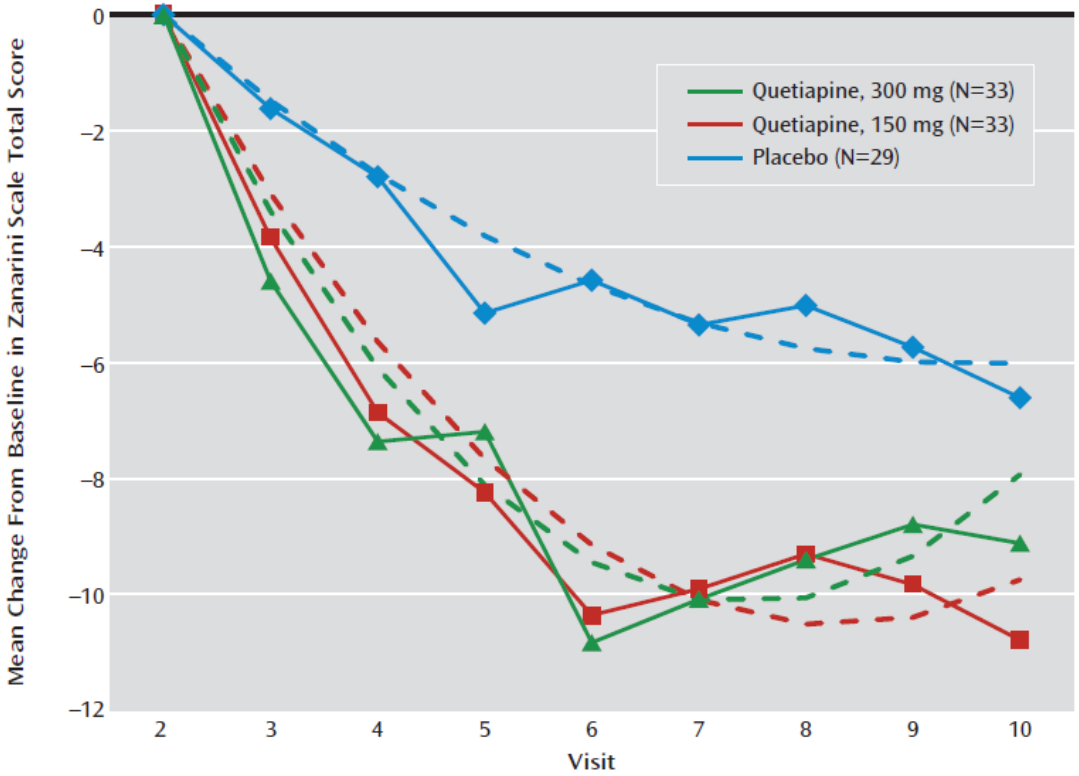
Olanzapine RCT #2: Mean Changes in ZAN- BPD Total Scores



Zanarini et al., 2011

Two Doses of Quetiapine vs. PLA in Changes in Patients with Borderline Personality Disorder

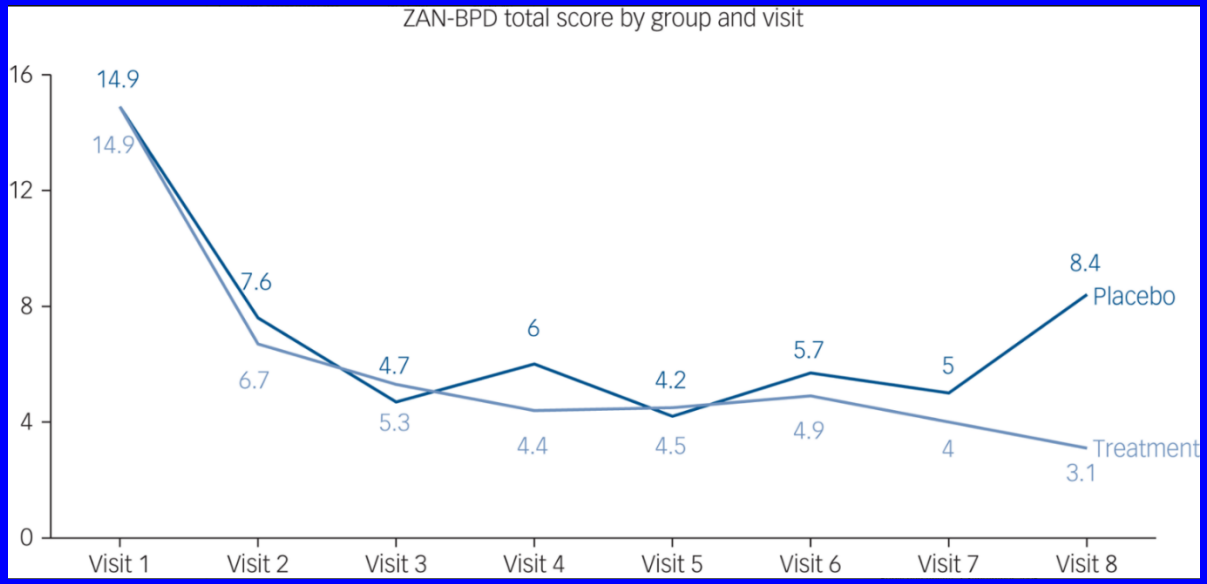
FIGURE 1. Changes in Mean Total Score on the Zanarini Rating Scale for Borderline Personality Disorder Among Study Participants Who Received Quetiapine or Placebo[a]



[a] Solid lines represent least-square mean estimates; dashed lines represent estimates from the shared parameter model with linear and quadratic effects. Results do not align completely because of differences in how group means are modeled and because the shared parameter model corrects for informative dropout.

Black et al, 2014

Brexpiprazole 1-2 mg vs. PLA using Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD)



Grant et al. 2022

Borderline P D: PharmacoRxic Approaches III:SSRIs

- Many open label positive reports
- Only two RCTs (one published), both with fluoxetine
  - Overall, little data showing efficacy
- Clinical experience better

Borderline Personality Disorder: Other Approaches

- MAOIs- two DB studies
  - Cowdry and Gardner (1988)-TCP + in improving mood and and anxiety sx
  - Soloff et al (1993)- modest effect of PHEN
  - Parsons et al (1989)- PHEN helpful for atypical depression plus BPD
- Lithium
  - Sheard (1976) DB/PC- + effect in decreasing imp/agg behaviors in prisoners
  - Links et al (1990)- modest effect in decreasing anger and suicidal sx

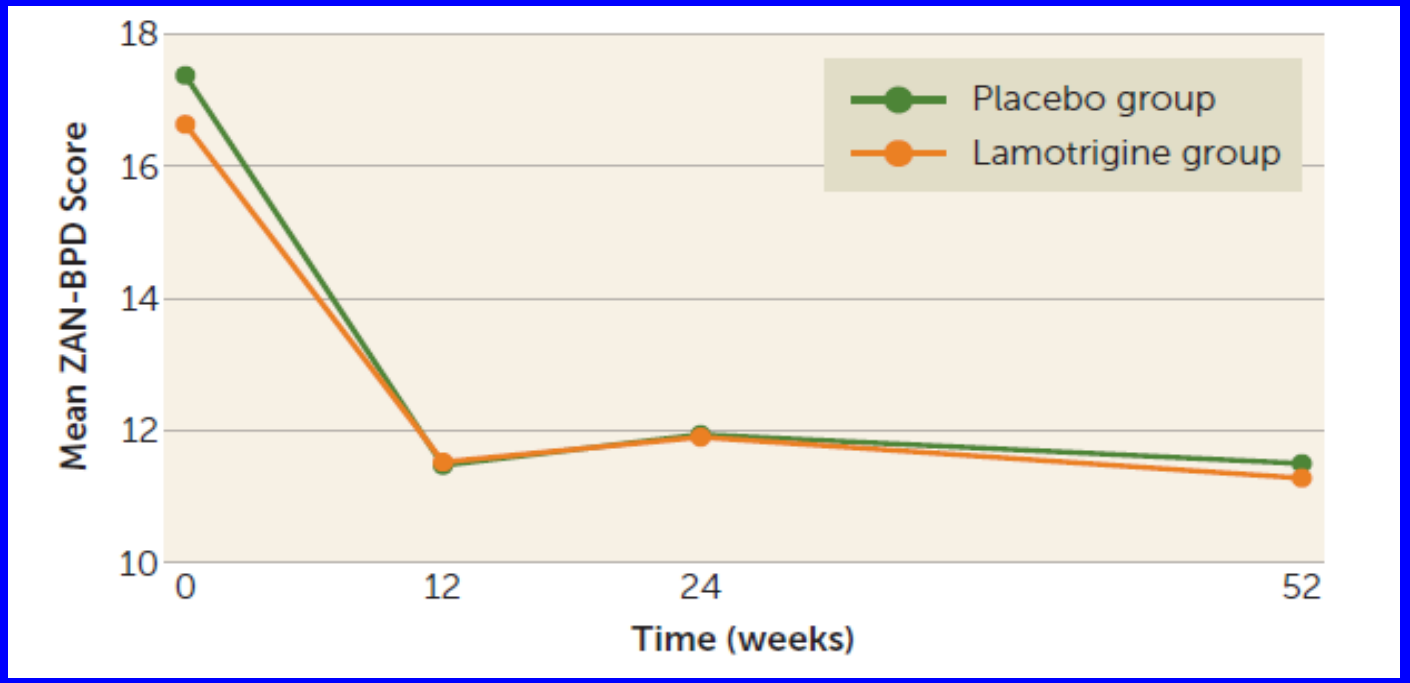
Borderline Personality Disorders: Anticonvulsants

- Earlier meta-analysis
  - TPX, LTG, VPA, OXC
  - Very + for impulsive behavioral dyscontrol (ES=1.51) and anger (ES=1.33)
    - » Lesser effects on depression and anxiety (ES=0.55 and 0.8)
- More recent meta-analysis (Gartlehner et al, 2021)- 9 studies-found no consistent positive effect

Lamotrigine for Borderline PD

- Two small studies suggesting efficacy (Tritt et al, 2005; Reich et al, 2009), targeting affective instability
- Third, largest study (Crawford et al, 2018): n=276, DB/PC, dose up to 400 mg for one year
  - Other TAU (meds and/or therapy) OK
  - No evidence of efficacy
    - » Only 34% subjects were taking meds adherently throughout study
  - ?More complex ill pts compared to prior studies?
- Conclusion- no evidence of efficacy (Pahwa et al, 2020)

Borderline Personality Disorder: Lamotrigine vs. PLA



Crawford et al, 2018

Borderline PD PharmacoRx: Anticonvulsants II: Topiramate

- Three DB studies, all from same group
- Nickel et al, 2004; Nickel et al, 2005; Loew et al, 2006
  - N=29, 56, 44
  - Up to 200-250 mg
  - Study 1-Improvement in anger, especially after week 4
    - » Dose vs. delayed effect
  - Study 2- Improvement in many parameters (but not depression or psychosis)
  - Study 3- males, difference in anger
- Weight loss-Mean difference=5-11 lbs
- Usual side effects
- Open followup of study 2 shows continued benefit over 18 mos (Nickel, 2007)

Proposed Borderline Subtypes

- Subtype
  - Hysteroid dysphoric
  - Schizotypal
  - Impulsive
  - Empty depressive
- Med Strategy
  - SSRIs, MAOIs
  - Antipsychotic
  - Anticonvulsants, SSRI, SGAs, lithium
  - Unknown
- No evidence for targeted interventions

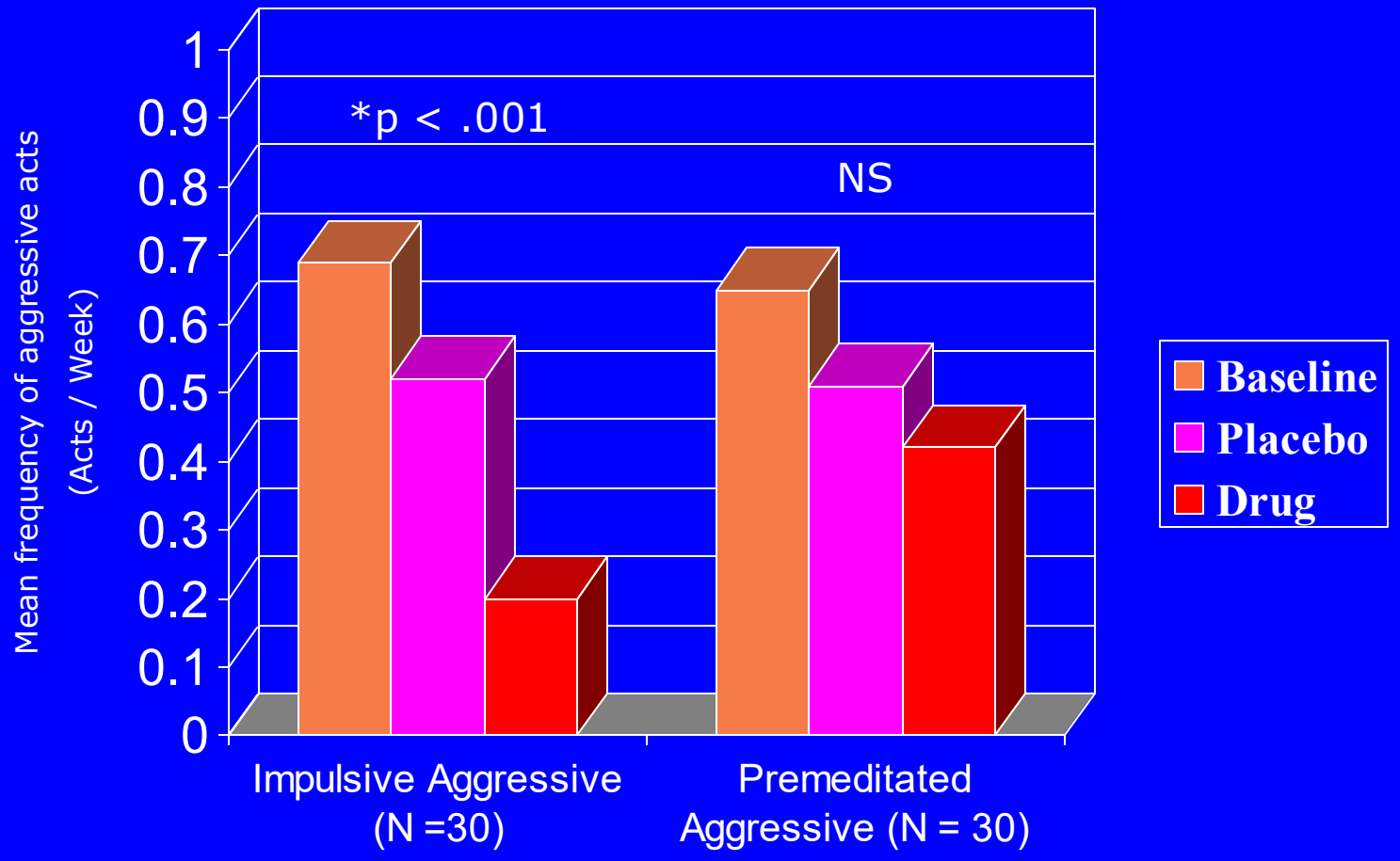
Controversial Rxes for Borderline PD

- Ketamine: Three studies
  - N=22 RCT, IV ketamine (0.5 mg/kg) vs. midazolam (Fineberg et al, 2023)
    - » Numerical, not statistical advantage for ketamine for depression, suicidal ideation and other measures
  - N=100; TRD + vs- BPD
    - » No difference in outcome (Danayan et al, 2023)
  - N=153; BPD features did not affect outcome of IV ketamine (Chen et al, 2022)
- Psychedelics (Carrithers et al, 2025)
  - Old data on antisocial PD/psychopathy
  - Recent small case series on Cluster B PDs

PharmacoRx of Impulsive/ Aggressive Behaviors I

- Most studies not in PD patients
- Earlier studies on carbamazepine, phenytoin, lithium, beta blockers
- Mood stabilizers
  - Lithium in prisoners (1976)
  - Phenytoin 300 mg in DB/PC study decreased impulsive aggression in prisoners (Barratt et al, 1997)

Effect of Phenytoin on Impulsive and Premeditated Aggression in Prison Inmates



Barratt et al. 1997

Pharmacotherapy of Aggressive Behavior II: (Comai et al, 2012)

- Multiple RCTs supporting
  - SGAs
  - Anticonvulsants (lamotrigine, valproate, topiramate, gabapentin)
  - Lithium
- Consistent positive effects seen

PharmacoRx of Impulsive/ Aggressive Behaviors IV

- SSRIs
  - FLU vs. PLA in 100 IEDs-+ effect, not related to plasma level (Coccaro et al, 2009)
  - PAR decreased suicidal behavior in DB study
  - PAR 20 mg reduced negative affect and hostility and increased sociability in DB study of normals (Knutson et al, 1998)
    - » Effects correlated with PAR levels
  - CIT, but not reboxetine abolished startle response to negative affective images in normals (Harmer et al, 2004)
- Opiate antagonists-naltrexone for SIB?

PharmacoRx of Impulsive/ Aggressive Behaviors V

- Consider comorbid disorders
  - Drug/Etoh abuse
  - ADHD?
    - » Impulsive behavior in rats reduced by amphetamine and methylphenidate (Evenden and Ko, 2005)

Management Issues in the PharmacoRx of Borderline PD

- Setting appropriate expectations
- Difficulty evaluating efficacy
- Psychodynamic considerations for pharmacoRx
- Compliance issues
- Drug/Etoh abuse

Summary

- Conceptual framework for personality disorders- dimension vs. categorical- in dispute
- Recent followup studies indicate better syndrome than typically imagined
  - Functional outcome less sanguine
- Meds generally not recommended by all recent reviews/Practice Guidelines
  - Nonetheless, most useful meds-SGAs, anticonvulsants
  - Major efficacy in anger/irritability/impulsivity
  - ?Affective lability
  - Caution re:polypharmacy
- Optimal management probably therapy plus meds