Borderline Personality Disorder (BPD) Clinical Development – Methodological Issues

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BPD Clinical Development – Methodological Issues

- No approved therapies & several failed trials
- Lack of ‘gold standard’ measure
- Uncertain placebo rate
- Phase II sample sizes that mirror Phase III
- Difficult and non-adherent population
- Timing of the Primary Endpoint
- What about psychotherapy?

BPD – No Approved Therapies & Several Failed Trials

17 Studies found for: **Interventional Studies | Borderline Personality Disorder | Industry**

Also searched for **Borderline Personality** and **Diseases**. See Search Details

Applied Filters: ☑ Interventional ☑ Funding: Industry

List | By Topic | On Map | Search Details

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Showing: 1-17 of 17 studies 25 studies per page

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Status

Recruitment:
- ☐ Not yet recruiting
- ☐ Recruiting
- ☐ Enrolling by invitation
- ☐ Active, not recruiting
- ☐ Suspended
- ☐ Terminated
- ☐ Completed
- ☐ Withdrawn
- ☐ Unknown status†

Expanded Access:

Eligibility Criteria

Age: ____ years OR Age Group
- ☐ Child (birth–17)
- ☐ Adult (18–64)
- ☐ Older Adult (65+)

Sex:
- ◉ All
- ○ Female
- ○ Male

☐ Accepts Healthy Volunteers

Study Type
- ○ All
- ◉ Interventional (Clinical Trial)
- ○ Observational
- ○ – Patient Registries
- ○ Expanded Access

Study Results

Study Phase

Funder Type
- ☐ NIH
- ☐ Other U.S. Federal agency
- ☑ Industry
- ☐ All others (individuals, universities, organizations)

Study Documents

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Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	A Trial of Brexpiprazole in the Treatment of **Borderline Personality Disorder**	• **Borderline Personality Disorder**	• Drug: Brexpiprazole • Other: Placebo	• For additional information regarding sites, contact 844-687-8522 New York, New York, United States
2	☐	Recruiting	Evaluating the Safety and Tolerability of Brexpiprazole in the Treatment of Adults With **Borderline Personality Disorder**	• **Borderline Personality Disorder**	• Drug: Brexpiprazole	• For additional information regarding sites, contact 844-687-8522 New York, New York, United States
3	☐	Completed	Olanzapine in Patients With **Borderline Personality Disorder**	• **Borderline Personality Disorder**	• Drug: Olanzapine • Drug: placebo	• For additional information regarding investigative sites for this trial, contact 1-877-CTLILLY (1-877-285-4559, 1-317-615-4559) Monday-Friday from 9:00 AM to 5:00 PM Eastern Time (UTC/GMT - 5 hours, EST), or speak with your personal physician Atlanta, Georgia, United States • For additional information regarding investigative sites for this trial, contact 1-877-CTLILLY (1-877-285-4559, 1-317-615-4559) Monday-Friday from 9:00 AM to 5:00 PM Eastern Time (UTC/GMT - 5 hours, EST), or speak with your personal physician Marietta, Georgia, United States • For additional information regarding investigative sites for this trial, contact 1-877-CTLILLY (1-877-285-4559, 1-317-615-4559) Monday-Friday from 9:00 AM to 5:00 PM Eastern Time (UTC/GMT - 5 hours, EST), or speak with your personal physician Minneapolis, Minnesota, United States • (and 36 more...)
4	☐	Completed	Efficacy and Safety of Olanzapine in Patients With **Borderline Personality Disorder**	• **Borderline Personality Disorder**	• Drug: Olanzapine	• For additional information regarding investigative sites for this trial, contact 1-877-CTLILLY (1-877-285-4559, 1-317-615-4559) Mon-Fri from 9 AM to 5 PM Eastern Time (UTC/GMT - 5 hours, EST), or speak with your personal physician National City, California, United States • For additional information regarding investigative sites for this trial, contact 1-877-CTLILLY (1-877-285-4559, 1-317-615-4559) Mon - Fri from 9 AM to 5 PM Eastern time (UTC/GMT - 5 hours, EST), or speak with your personal physician New Haven, Connecticut, United States • For additional information regarding investigative sites for this trial, contact 1-877-CTLILLY (1-877-285-4559, 1-317-615-4559) Mon-Fri from 9 AM to 5 PM Eastern Time (UTC/GMT - 5 hours, EST), or speak with your personal physician Indianapolis, Indiana, United States • (and 12 more...)
5	☐	Completed	Verkes **Borderline** Study: The Effect of Quetiapine on **Borderline Personality** Disordered Patients	• **Borderline Personality Disorder**	• Drug: Quetiapine fumarate • Drug: Placebo	• Research Site Apeldoorn, Netherlands • Research Site Nijmegen, Netherlands • Research Site Veghel, Netherlands
6	☐	Completed	Evaluating an Internet-Based Self-Management Intervention for **Borderline**	• **Borderline Personality Disorder**	• Behavioral: Priovi • Other: CAU	• Gaia AG Hamburg, Germany
7	☐	Recruiting	Brexpiprazole in **Borderline Personality Disorder**	• **Borderline Personality Disorder**	• Drug: Rexulti • Drug: Placebo	• University of Chicago Chicago, Illinois, United States
8	☐	Completed	Study of Lamotrigine Treatment of Affective Instability in **Borderline Personality Disorder**	• **Borderline Personality Disorder**	• Drug: Lamotrigine • Drug: Placebo	• McLean Hospital Belmont, Massachusetts, United States
9	☐	Completed	Effective Measurement of Risperidone Treatment Outcome for Persons With **Borderline Personality Disorder**	• **Borderline Personality Disorder**	• Drug: risperidone	• University of Alabama at Birmingham Birmingham, Alabama, United States
10	☐	Completed	Quetiapine Treatment for Symptoms Associated With **Borderline Personality Disorder**	• **Borderline Personality Disorder**	• Drug: Quetiapine Fumarate	• University of Medicine and Dentistry of New Jersey - School of Osteopathic Medicine - Department of Psychiatry Cherry Hill, New Jersey, United States
11	☐	Completed Has Results	PET Imaging and Olanzapine Treatment in **Borderline Personality Disorder**	• **Borderline Personality Disorder**	• Drug: olanzapine	• University of Minnesota, Dept of Psychiatry Minneapolis, Minnesota, United States
12	☐	Completed	Depakote ER in **Borderline Personality Disorder**	• **Borderline Personality Disorder**	• Drug: Depakote ER	
13	☐	Recruiting	Effectiveness of PTSD-treatment Compared to Integrated PTSD-PD-treatment in Adult Patients With Comorbid PTSD and BPD	• Posttraumatic Stress **Disorder** (PTSD) • **Borderline Personality Disorder** (BPD)	• Behavioral: EMDR • Behavioral: DBT	• Sinai Centrum Amstelveen, Noord-Holand, Netherlands
14	☐	Completed Has Results	Seroquel Extended Release (XR) for the Management of **Borderline Personality Disorder** (BPD)	• **Borderline Personality Disorder**	• Drug: quetiapine extended-release • Drug: Placebo	• University of Iowa, Department of Psychiatry Iowa City, Iowa, United States • McLean Hospital, Harvard Medical School, Department of Psychiatry Belmont, Massachusetts, United States • University of Minnesota Medical Center, Fairview Riverside Minneapolis, Minnesota, United States
15	☐	Completed	Ziprasidone in the Treatment of **Borderline Personality Disorder**	• **Borderline Personality Disorder**	• Drug: ziprasidone • Drug: Placebo	• Department of Psychiatry, Sta. Creu and St. Pau Hospital Barcelona., Spain
16	☐	Completed	Calling for Care: Cell Phones for Mood Telemetry in Teens	• Bipolar **Disorder** • Cyclothymia • **Borderline Personality Disorder**	• Other: Mental health telemetry (MHT)	• Sunnybrook Health Sciences Centre Toronto, Ontario, Canada
17	☐	Completed Has Results	Safety and Efficacy Study of Citalopram and Lithium for the Treatment of Depressive Mood **Disorder** Symptoms	• Major Depressive **Disorder** • Dysthymia • Depression Not Otherwise Specified • **Borderline Personality Disorder**	• Drug: Lithium Carbonate • Drug: Placebo • Drug: Citalopram	• Artemis Institute for Clinical Research San Diego, California, United States • Northwest Clinical Research Center Bellevue, Washington, United States

BPD – No Approved Therapies & Several Failed Trials

- ClinicalTrials.gov – 17 Clinical Trials w/Industry funding
  - 14/17 involve Investigational Medicinal Product (IMP)
  - 3/17 include behavioral interventions
- 14/17 trials have Completed
  - 11/14 involving IMP
  - 3/3 including behavioral interventions
- Completed Clinical Trials explored:
  - Citalopram & Lithium*
  - Mental Health Telemetry
  - Ziprasidone
  - Seroquel XR
  - EMDR/DBT
  - Depakote IR
  - Olanzapine
  - Quetiapine
  - Risperidone
  - Lamotrigine
  - Internet-Based Self-Management
- No approved drug therapies to-date
- 3 Ongoing Clinical Trials with Brexpiprazole

*Trial included MDD, Dysthymia, Depression NOS and/or BPD patients

BPD – Lack of ‘Gold Standard’ Measure

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- There is no clear consensus on a ‘gold standard’ measure in BPD
  - Several sponsors have leveraged the Zanarini Rating Scale for BPD (ZAN-BPD)
  - However, no trials have led to a drug approval with the ZAN-BPD as the primary or secondary endpoint.
  - Is a scale with a one-week recall period (i.e., aligned with the frequency of psychotherapy visits) suitable for clinical trials with longer recall periods?

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  - Is a scale with a one-week recall period (i.e., aligned with the frequency of psychotherapy visits) suitable for clinical trials with longer recall periods?
  - A few sponsors have used the Clinical Global Impression (CGI)
    - PRO – Regulatory accepted across trials & therapeutic areas
    - CON – Limited dynamic range of performance
  - No BPD trials have led to a drug approval with the CGI as the primary or secondary endpoint.
  - Is a scale with limited dynamic range suitable as a primary endpoint?

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Clinical Global Impression (CGI)

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed
   1 = Normal, not at all ill
   2 = Borderline mentally ill
   3 = Mildly ill
   4 = Moderately ill
   5 = Markedly ill
   6 = Severely ill
   7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
   Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed
   1 = Very much improved
   2 = Much improved
   3 = Minimally improved
   4 = No change
   5 = Minimally worse
   6 = Much worse
   7 = Very much worse

BPD – Lack of 'Gold Standard' Measure

Drug/Intervention	Primary Endpoint(s)	Key Secondary Endpoints
Brexpiprazole	ZAN-BPD	CGI; PGI
Brexpiprazole – Safety Study	Adverse Events (AEs)	
Brexpiprazole	ZAN-BPD	BEST; MOAS
Citaprolam & Lithium	S-STS	BHS; BSS
Depakote IR	SCL-90-R	Barratt Impulsivity Scale
EMDR/DBT	CAPS5	SCID-5-PD
Internet-Based Self-Management	BPD Severity Index	BPDCL – Short Version
Lamotrigine	ALS; Affective Lability of ZAN-BPD	Items of ZAN-BPD
Olanzapine	ZAN-BPD	
Olanzapine	ZAN-BPD	SDS; OAS-M; LSDS; Suicide Att.
Olanzapine – PET Study	PET metabolism	
Quetiapine	Psychotic-like symptoms & severity of psychiatric symptoms	Mood, Anger; Impulsiveness; Hostility; Anxiety
Quetiapine	SCL-90-R	Safety & Tolerability
Risperidone	CGI; BSI	BDI
Seroquel XR	ZAN-BPD; BEST; OAS-M; GAF; BIS; SCL-90-R; YMS; SDS	
Ziprasidone	CGI-BPD;	HAM-D-17; HAM-A; BPRS; SCL-90-R; BIS

ALS – Affective Lability Scale
BEST – Borderline Evaluation of Severity over Time
BDI – Beck Depression Inventory
BHS – Beck Hopelessness Scale
BIS – Barratt Impulsiveness Scale
BPDCL – Borderline Personality Disorder Checklist
BPRS = Brief Psychiatric Rating Scale
BSI – Brief Symptom Inventory
BSS – Beck Scale for Suicide Ideation
CAPS5 – Clinician Administered PTSD Scale for DSM-5
CGI – Clinician Global Impression
GAF – Global Assessment of Functioning
HAM-A – Hamilton Rating Scale for Anxiety
HAM-D-17 – Hamilton Rating Scale for Depression
LSDS – Lifetime Self-Destructiveness Scale
MOAS – Modified Overt Aggression Scale
OAS-M – Overt Aggression Scale – Modified
PGI – Patient Global Impression
SCL-90-R – Symptom Checklist 90 – Revised
SCID-5-PD – Structured Clinical Interview, DSM-5, Personality Disorders
SDS – Sheehan Disability Scale
S-STS – Sheehan-Suicidality Tracking Scale
Suicide Att. – Number of Suicide Attempts
YMS – Young Mania Rating Scale
ZAN-BPD – Zanarini Rating Scale for Borderline Personality Disorder

BPD – Uncertain Placebo Rate

- Lack of a ‘gold standard’ measure complicates establishing a placebo rate
- There is no established placebo rate in BPD Clinical Development
- Previous trials (e.g., olanzepine) have experienced high PBO rates

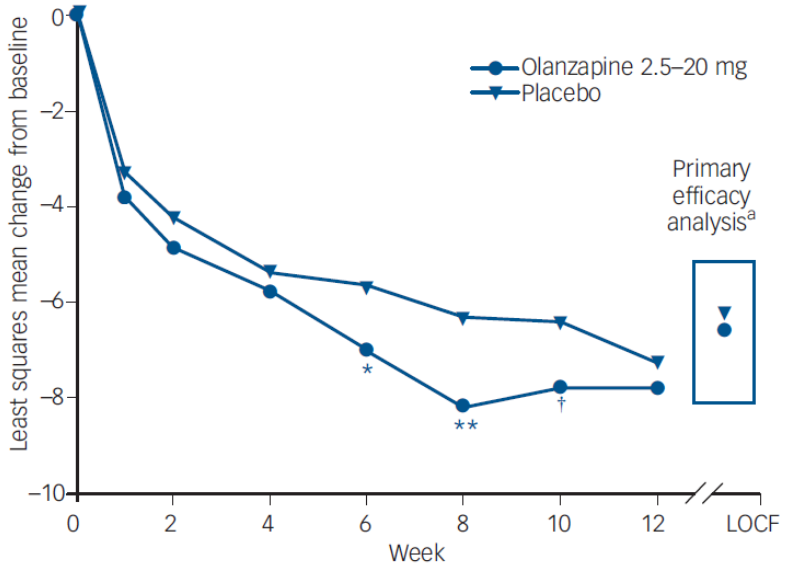

Fig. 2 Mean visit-wise changes in Zanarini Rating Scale for Borderline Personality Disorder (ZAN–BPD) total scores (mixed-effects model repeated measures), and mean baseline to end-point change in ZAN–BPD total score, last observation carried forward (LOCF).

a. Type III sum of squares (ANOVA): model = baseline, investigator, therapy; P=0.661.
*P<0.05; **P<0.01; †P=0.08.

The British Journal of Psychiatry (2008) 193, 485–492. doi: 10.1192/bjp.bp.107.037903

BPD – Lack of 'Gold Standard' Measure & Uncertain PBO Rate

- Potential Solutions:
  - Include a variety of measures in early phases of development
    - Phase Ib & Phase IIa to establish the PBO rate
    - Determine COA type that works best in population (PerfO, ClinRO, ObsRO, CRO)
  - Test drive measures with the intended population
  - Consider including quality of life and functional measures
    - Important to help demonstrate clinical meaningfulness
    - Eventual potential payer discussions
    - Avoid need to collect this data in Phase IIIb/IV trials
  - Develop your own measure – Agitation & Aggression Psychiatric Inventory© (AAPI©)
  - Include multiple or co-primary primary endpoints
  - If already in Phase IIb or Phase III consider using an adaptive trial design
    - Best shot on goal when variability around endpoints and PBO rate is uncertain
    - Allows you to drop endpoints (just like doses) for futility at planned analyses
    - Permits increasing the sample size if there is increased variability around the COA or a higher than expected PBO rate
    - NOTE: Always have fully transparent discussions with regulatory authorities around all reasons for leveraging an adaptive design

BPD – Phase II sample sizes that mirror Phase III

- Phase II BPD clinical trials have become increasingly large with sample sizes expected in Phase III
  - For instance, an enrolling Brexpiprazole, Phase II trial plans to enroll (N=240)
- This results from not having great data regarding:
  - COA performance (i.e., variability)
  - Placebo rate
    - Both are needed for power calculations and sample size determination
- Potential Solution:
  - Implement an adaptive trial design to allow:
    - Enrollment of a smaller sample
    - Dropping a dose for futility – subjects then roll into other arm increasing power
    - Potentially increasing sample at the IA when there is unexpected variability in PE or high PBO rate
    - Overall, an adaptive design is the best solution when you do not know COA performance or PBO rate in the intended population

BPD – Difficult & Non-Adherent Population

- According to the DSM-5, BPD patients must exhibit five or more of the following diagnostic criteria:
  - Frantic efforts to avoid real or imagined abandonment.
  - Pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
  - Identity disturbance: markedly and persistently unstable self-image or sense of self.
  - Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating).
  - Recurrent suicidal behavior, gestures, or threats, or self-mutilating behaviors.
  - Affective instability due to a marked reactivity of mood.
  - Chronic feelings of emptiness.
  - Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent fights).
  - Transient, stress-related paranoid ideation or severe dissociative symptoms.

BPD – Difficult & Non-Adherent Population

- In addition to meeting DSM-5 BPD criteria, this population:
  - Multiple comorbidities
    - ADHD
    - Depression
    - Bipolar Disorder
    - Anxiety
    - PTSD
    - Eating Disorders
    - Substance Abuse
  - Affectively unstable
  - Angry, agitated and aggressive population
  - Extremely impulsive
  - Frequently paranoid
  - High percentage of substance use and abuse
  - Do not like to be told what to do
  - Frantic efforts to avoid real or imagined abandonment

BPD – Difficult & Non-Adherent Population

- Potential Solutions:
  - Leverage sites with longstanding patient relationships to:
    - Increase trust and potentially decrease dropouts
    - Increase adherence
    - Decrease impulsivity
    - Improve the probability of following directions
    - Avoid feelings or real (i.e., the trial is ending) abandonment
  - Craft Inclusion & Exclusion criteria to allow for comorbidities, but only in treated and/or stable patients.
  - Leverage a run-in period, screen for illicit substances during and inform subjects they will be removed from the trial for illicit drug use during the trial.
  - Remove non-adherent patients – leverage monitored dosing strategy
  - Discuss and gain regulatory approval for exclusion of deliberately non-adherent subjects in the Per-Protocol Set (PPS) for the primary analyses

BPD – Timing of the Primary Endpoint (PE)

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- It is critical to think creatively around the timing of the PE
- Subjects may self-sabotage before and because of the trial ending
  - Stop taking their IMP
  - Dropout of the trial

BPD – Timing of the Primary Endpoint (PE)

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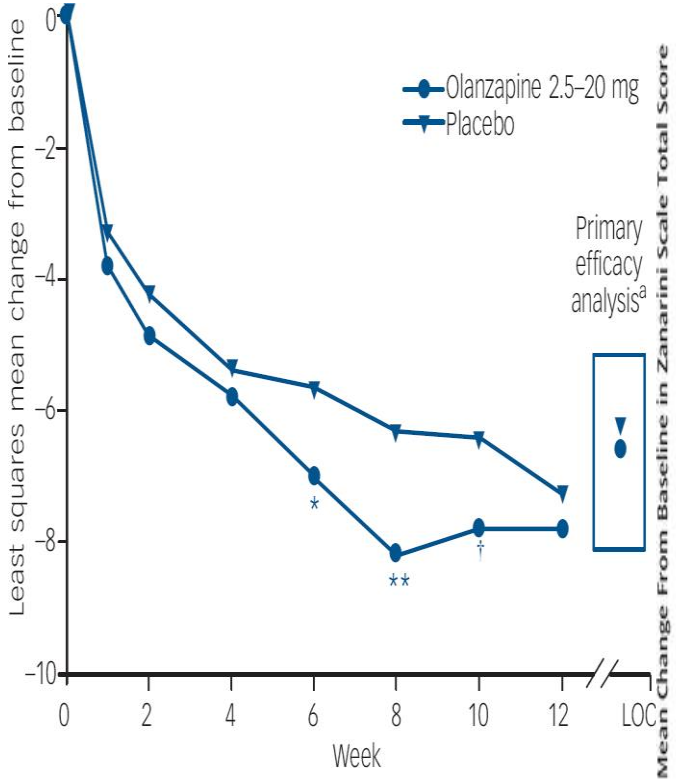
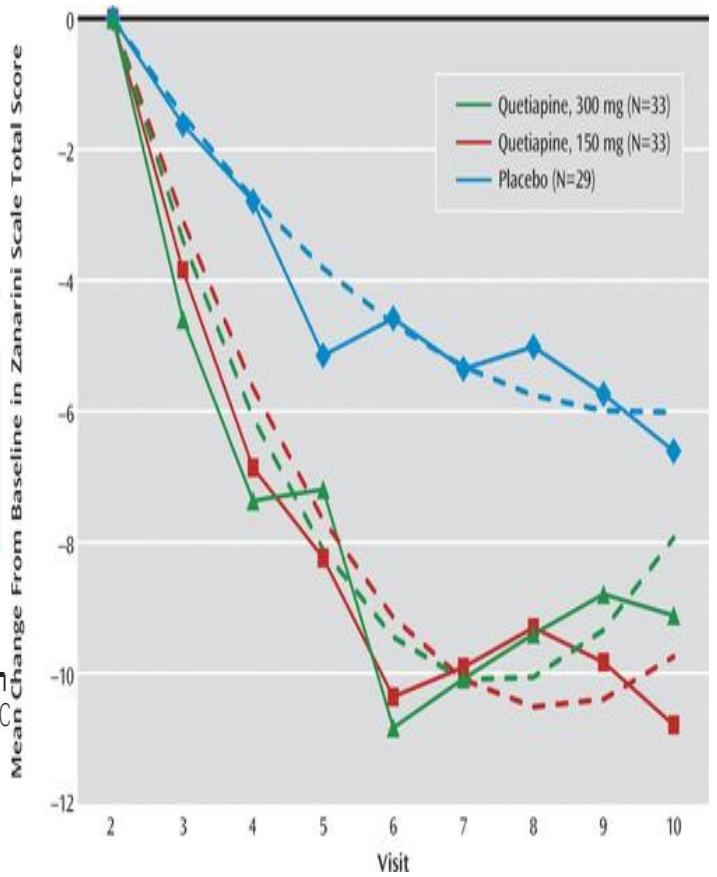
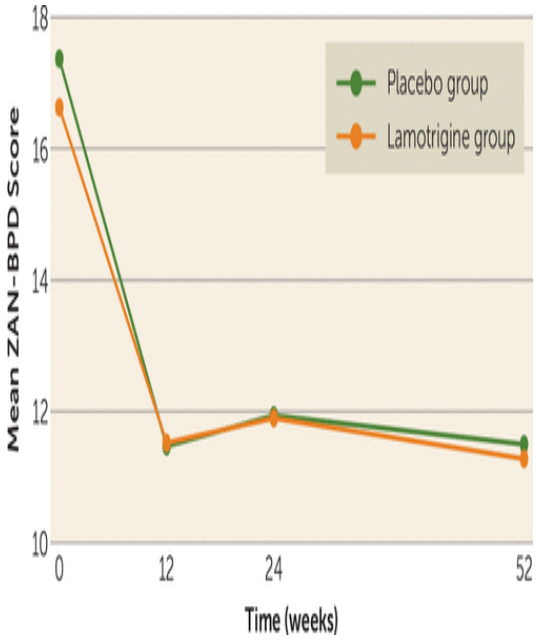


Schulz SC et al. Olanzapine for the treatment of borderline personality disorder 2008



Black et al. Comparison of **low and moderate dosages of extended-release quetiapine** in borderline personality disorder **2014**



Crawford M, et al. The Clinical Effectiveness and Cost-Effectiveness of **Lamotrigine** in Borderline Personality Disorder **2018**

BPD – Timing of the Primary Endpoint (PE)

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- Potential Solutions:
  - Extend trial and collect PE well before the last visit
  - Blind subjects and PIs on the timing of the PE
  - Collect PE at multiple time points
    - For example, if the goal is 12-weeks of treatment, then plan for 16-week trial to allow:
      - 2-week blinded PBO run-in period
      - 12 weeks of active treatment
      - 2-weeks of blinded safety follow-up
        - All subjects and PI believe the trial ends at week 16
      - Collection of PE every 2 weeks up to 16 weeks
      - Primary analysis: longitudinal mixed effects model evaluating difference at 12 weeks
        - Uses all PE data up to 12 weeks

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      - Primary analysis: longitudinal mixed effects model evaluating difference at 12 weeks
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  - Alternatively, select a different objective endpoint and consider leveraging a time to event analysis
    - Number of suicidal attempts, ER visits, Urgent Care visits, psychiatric inpatient hospitalizations, Primary Care Physician visits, and/or non-suicidal self-injuries
    - Measure time to trial dropout resulting from these events

BPD – What about Psychotherapy?

- Psychotherapy is standard of care in BPD
- How do you run a trial in BPD and ethically exclude the only SOC?
  1. Carefully, after discussions and alignment with regulators.

     OR
  2. You allow psychotherapy, with limits defined in the protocol.
- Potential Solution:
  - Treat psychotherapy like an allowed concomitant medication.
  - Enrolled subjects must maintain their Pre-Screening psychotherapy.
  - Subjects cannot start psychotherapy within a specified time prior to enrollment.
  - Subjects cannot initiate psychotherapy during the trial.
  - Subjects who start the trial while in psychotherapy must remain in therapy throughout the trial.

BPD Clinical Development – Methodological Issues

Overall, given all the methodological issues reviewed in this presentation leaves one wondering whether the lack of an approved drug for BPD is because:

- Lack of a ‘gold standard’ measure
  - The COAs used as the primary and/or secondary endpoints
- Uncertain placebo rate
  - Lack of a ‘gold standard’ measure complicates establishing a placebo rate
  - High placebo rates seen in previous BPD clinical trials
- BPD subjects are a difficult and non-adherent population
- Study design
  - Inclusion/Exclusion criteria
  - Timing of the PE
- Study conduct
  - Addressing illicit substance use and abuse
  - Handling of deliberately non-adherent subjects
- Were the drugs studied, just not the right ones

Summary BPD Methodological Issues - Solutions

Lack of 'gold standard' measure, unknow PBO rate & Phase II sample sizes that mirror Phase III

- Employ a variety of measures in early phases of development
    - Phase Ib & Phase IIa to establish the PBO rate
- Test drive measures with the intended population
- Consider including quality of life and functional measures
    - Important for clinical meaningfulness
    - Eventual potential payer discussions
    - Avoid need to collect this data in Phase IIIb/IV trials
- Consider including multiple or co-primary primary endpoints
- If already in Phase IIb or Phase III consider using an adaptive trial design to allow:
    - Enrollment of a smaller sample
    - Dropping a dose for futility – subjects then roll into other arm increasing power
    - Potentially increasing sample with unexpected variability in PE or higher than expected PBO rate
    - An adaptive design is the best solution when you do not know COA performance or PBO rate in intended population

Difficult and non-adherent population

- Leverage sites with longstanding patient relationships to:
    - Increase trust and potentially decrease dropouts
    - Increase adherence
    - Decrease impulsivity
    - Improve probability of following directions
    - Avoid feelings or real (i.e., the trial is ending) abandonment
- Craft Inclusion & Exclusion criteria to allow for comorbidities, but only in treated and/or stable patients.
- Leverage a run-in period, screen for illicit substances during and inform subjects they will be removed from the trial for illicit drug use.
- Remove non-adherent patients
- Discuss and gain regulatory approval for their exclusion in the Per-Protocol Set (PPS) for the primary analyses

Summary BPD Methodological Issues – Solutions (Continued)

Timing of the Primary Endpoint

- Extend trial and collect PE well before the last visit
- Blind subjects and PIs on the timing of the PE
- Collect PE at multiple time points
  - For example, if the goal is 12-weeks of treatment, then plan for 16-week trial to allow:
    - 2-week blinded PBO run-in period, 12 weeks of treatment
    - Collection of PE every 2 weeks up to 16 weeks
    - Primary analysis: longitudinal mixed effects model evaluating difference at 12 weeks
      - Uses all PE data up to 12 weeks

What about Psychotherapy?

- Treat psychotherapy like an allowed concomitant medication.
- Enrolled subjects must maintain their Pre-Screening psychotherapy.
- Subjects cannot start psychotherapy within a specified time prior to enrollment.
- Subjects cannot initiate psychotherapy during the trial.
- Subjects who start the trial while in psychotherapy must remain in therapy throughout the trial.