Treatment of Borderline Personality Disorder:
A Regulator's Perspectives

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—no conflicts of interest to disclose—

Disclaimer

The views expressed in this presentation are the personal views of the speaker.

They should *not* be understood or quoted as being made on behalf of or reflecting the position of the FDA.

"Is (Borderline) Personality Amenable to Pharmacotherapy (APT)?"

- Complex network of deficits:

  Find a hub → find a drug

- But maybe not in isolation → combine with learning to change higher order function
- Evidence for "APT"ness of personality
  - SUD → apparent personality change
  - SSRI → acute shift in attentional bias in healthy volunteers*

*Harmer, C. J., & Cowen, P. J. (2013). 'It's the way that you look at it'—a cognitive neuropsychological account of SSRI action in depression. Philosophical Transactions of the Royal Society B: Biological Sciences, 368(1615), 20120407.

So why do drug trials for BPD tend to fail?

Maybe not because of

- Dropout/non-adherence

Example: Clinical review of vortioxetine for MDD:

Table 35: Subject Disposition - Study 315 (US)

	Treatment n (%)				
	Placebo	LuAA21004		Duloxetine	
		15 mg	20 mg	60 mg	Total
Randomized (a)	161 (100)	147 (100)	154 (100)	152 (100)	614 (100)
Treated	159 (98.8)	147 (100)	154 (100)	150 (98.7)	610 (99.3)
Completed study	129 (80.1)	113 (76.9)	113 (73.4)	115 (75.7)	470 (76.5)
Early termination	32 (19.9)	34 (23.1)	41 (26.6)	37 (24.3)	144 (23.5)
Primary reasons for early termination					
Adverse events	4 (2.5)	14 (9.5)	14 (9.1)	10 (6.6)	42 (6.8)
Lack of efficacy	9 (5.6)	0	2 (1.3)	1 (0.7)	12 (2.0)
Noncompliance	1 (0.6)	3 (2.0)	4 (2.6)	1 (0.7)	9 (1.5)
Protocol deviations	4 (2.5)	3 (2.0)	3 (1.9)	2 (1.3)	12 (2.0)
Withdrawal of consent	5 (3.1)	5 (3.4)	4 (2.6)	6 (3.9)	20 (3.3)
Lost to follow-up	8 (5.0)	8 (5.4)	11 (7.1)	15 (9.9)	42 (6.8)
Other	1 (0.6)	1 (0.7)	3 (1.9)	2 (1.3)	7 (1.1)
FAS	153	145	147	146	591

Source: Table 2.q, page 57/185 of 2.7.3 Summary of Clinical Efficacy
(a) Percentages are based on all randomized subjects.

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Review

Treatment completion in psychotherapy for borderline personality disorder – a systematic review and meta-analysis

Barnicot K, Katsakou C, Marougka S, Priebe S. Treatment completion in psychotherapy for borderline personality disorder – a systematic review and meta-analysis.

Objective: Psychotherapy for borderline personality disorder (BPD) has been associated with problematically low treatment completion rates.
Method: PsycInfo and Medline were systematically searched to identify studies providing information on treatment completion in psychotherapy models that have been shown to be effective for BPD. A meta-analysis of treatment completion rates and a narrative analysis of factors predicting dropout were conducted.
Results: Forty-one studies were included, with completion rates ranging from 36% to 100% – a substantial between-study heterogeneity. Random effects meta-analyses yielded an overall completion rate of 75% (95% CI: 68–82%) for interventions of < 12 months duration, and 71% (95% CI: 65–76%) for longer interventions. Egger's test for publication bias was significant for both analyses ($P \leq 0.01$). Study characteristics such as treatment model and treatment setting did not explain between-study heterogeneity. In individual studies, factors predicting dropout status included commitment to change, the therapeutic relationship and impulsivity, whilst sociodemographics were consistently non-predictive.
Conclusion: Borderline personality disorder should no longer be associated with high rates of dropout from treatment. However, the substantial variation in completion rates between studies remains unexplained. Research on the psychological processes involved in dropping out of treatment could further improve dropout rates.

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Key words: psychotherapy; borderline personality disorder; patient dropouts; meta-analysis

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Summations

- This is the first systematic review and meta-analysis of treatment completion rates in borderline personality disorder, focussing on psychotherapy models that have been demonstrated to be effective for this patient group
- The finding that on average 75% of patients complete treatment challenges the association of borderline personality with poor treatment completion rates
- Evidence on predictors of dropout was minimal

Maybe <u>not</u> because of

- Dropout/non-adherence

Example: Clinical review of brexpiprazole for SCZ:

NDA 205422

Rexulti® (Brexpiprazole tablets)

Table 28: Disposition of Subjects in Study 331-10-231

Subjects	Brexpiprazole 0.25 mg N=90 n (%)[a]	Brexpiprazole 2 mg N=182 n (%)[a]	Brexpiprazole 4 mg N=180 n (%)[a]	Placebo N=184 n (%)[a]	Total N=636 n (%)[a]
Randomized	90 (100)	182 (100)	180 (100)	184 (100)	636 (100)
Completed	56 (62.2)	124 (68.1)	121 (67.2)	109 (59.2)	410 (64.5)

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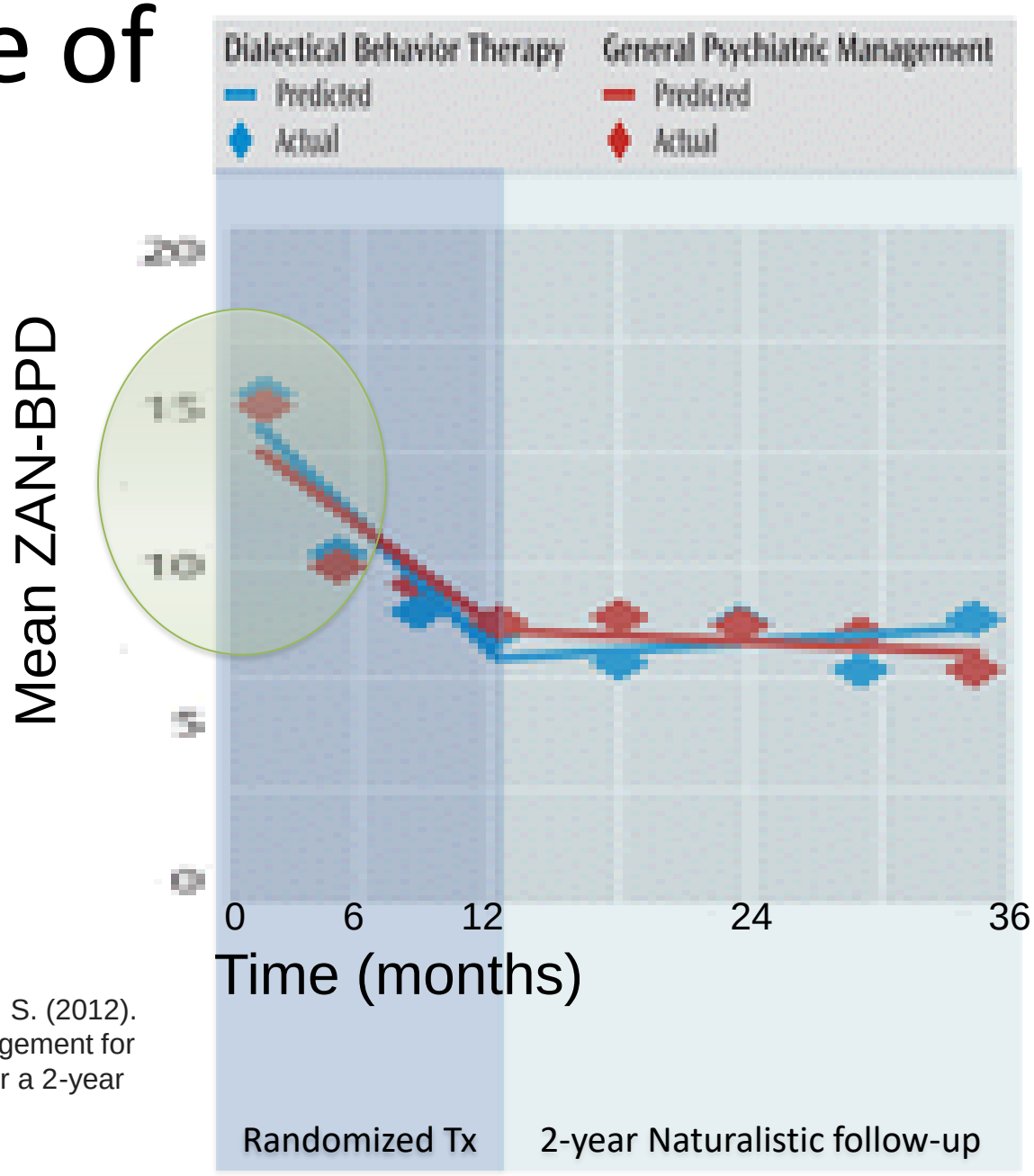
Maybe not because of

- Measure insensitivity
  - Robust change w/ high-level treatment (both arms including therapy and pharmacotherapy)…over 6 months of study treatment
  - …but possible 3 month trials too short to detect clinically meaningful change



McMain, S. F., Guimond, T., Streiner, D. L., Cardish, R. J., & Links, P. S. (2012). Dialectical behavior therapy compared with general psychiatric management for borderline personality disorder: clinical outcomes and functioning over a 2-year follow-up. *American Journal of Psychiatry*, *169*(6), 650-661.

Best Guesses

- Wrong meds
- Population heterogeneity in symptomatic targets
- Stigmatization → Insufficient/negative subject engagement

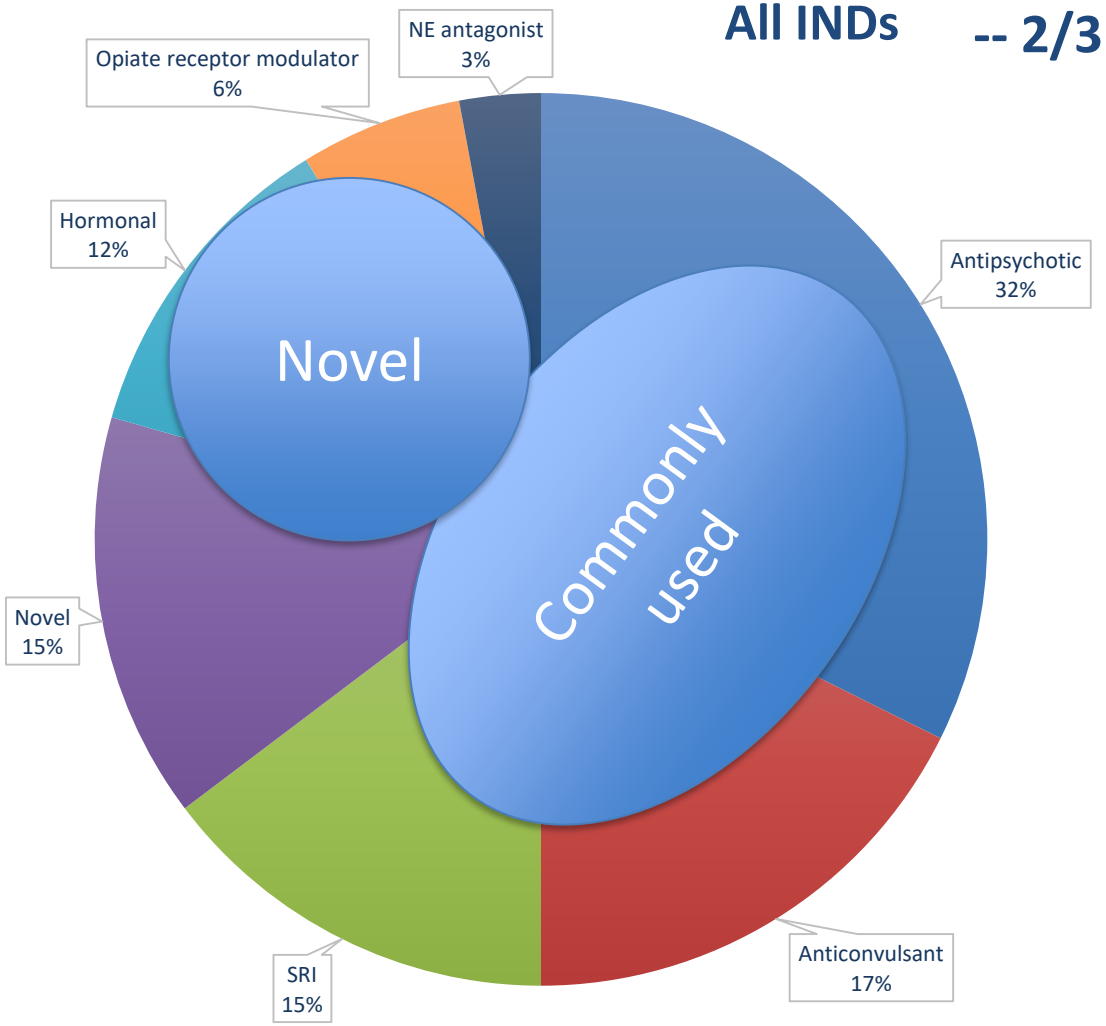
Wrong Meds – "Real world evidence"

- Polypharmacy common, stable over time
- rates similar to acute inpatient treatment of mania:
  - ~40% ≥3 concurrent standing medications
  - ~20% taking ≥4
  - ~10% taking ≥5

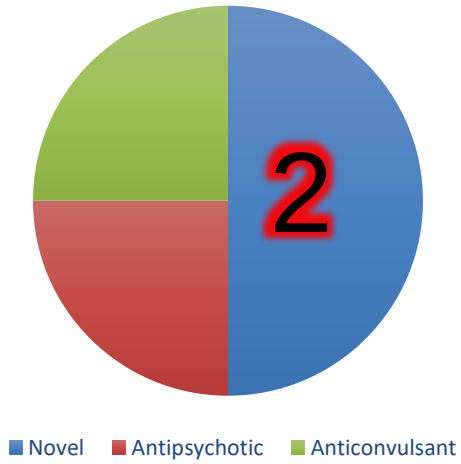
Sachs, G. S., et al. "Polypharmacy and bipolar disorder: what's personality got to do with it?." *International Journal of Neuropsychopharmacology* 17.7 (2014): 1053-1061.
Golden, J. C., Goethe, J. W., & Woolley, S. B. (2017). Complex psychotropic polypharmacy in bipolar disorder across varying mood polarities: a prospective cohort study of 2712 inpatients. *Journal of Affective Disorders*, *221*, 6-10.
Zanarini, M. C., Frankenburg, F. R., Hennen, J., & Silk, K. R. (2004). Mental health service utilization by borderline personality disorder patients and Axis II comparison subjects followed prospectively for 6 years. *The Journal of clinical psychiatry*.

Wrong Meds – Trials Limited

All INDs **-- 2/3 have been "usual suspects"**



Commercial INDs **-- few tries**



Antipsychotic Anticonvulsant SRI Novel Hormonal Opiate receptor modulator NE antagonist

Stigma & missed opportunities?

Examples:

- Rejection sensitivity
  - capacity for powerful positive emotion
  - if targeted, end of trial may present stressor that increases assay sensitivity

- Unstable/intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation
  - sensitive and passionate, idealistic
  - distinctive symptom less subject to confounding by comorbidity
  - involves higher-level processes → synergistic effects w/ psychotherapy?

Endpoints – Feeling, Functioning, Surviving

- Should be well-constructed/validated – FDA Guidance on PRO qualification highlights important considerations
- Measure should be able to capture severity independent of presence of e.g., MDD/GAD
- Digital measures, biomarkers, PerfROs could be promising, esp. in P1/2
- Critical Event-based outcomes could be good in P2/3

Missing data and intercurrent events

Q: How to handle missing data?

High Dropout rate expected in BPD? Methods of imputation?

- Critical to carefully define Estimand
- It is an empirical question to what extent drop out and loss to follow-up is representative of Tx failure
- A guess: BPD intermediate between SCZ (D.O.→ Tx failure) and MDD (MAR supported)

Missing data and intercurrent events

Q: What is your perspective on how medication compliance should be factored into the primary analysis for BPD trials?

ITT analysis will have diluted treatment effect?

Thoughts on subsetting primary analysis to only include those who have a certain level of compliance (e.g. at least 1 dose or more of randomized treatment, percentage of total medication adherence)?

- ITT underestimates ideal effect, estimates expected effect at point of Rx
- Preserving randomization of baseline characteristics critical to unbiased effect estimation:
  - randomization (loss can't be remedied) > power (loss can be remedied)

Conclusions

- AP/AD/AC meds have shown little evidence for efficacy but widely used (often in combination)
- Multimodal treatments may enhance retention

  & treatment effects could (even) be synergistic, increasing rather than decreasing assay sensitivity
- Interesting, novel approaches on horizon – & more are welcome!
- Patient population can be worked with much more than believed
- Encourage pre-competitive collaboration on endpoint development including patient engagement to identify meaningful treatment targets

https://commons.wikimedia.org/wiki/File:Hephthalite_horseman_on_British_Museum_bowl_460-479_CE.jpg

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