Pharmacotherapy in personality disorders? What the faq!
What you need to know in split treatment

Theo Ingenhoven, psychiatrist
Arkin, Amsterdam
Pharmacotherapy and/or psychotherapy for Borderline PD??

- No RCT’s that randomized psychotherapy and pharmacotherapy
- So, we don’t know what is best: one of them? to combine both? or not at all?

- A lot of evidence for efficacy psychotherapy in BPD (TFP, MBT, DBT, SFT...)
- Guidelines advocate psychotherapy as first choice! “Whenever possible”
- But.....
- Psychotherapy is not always possible (yet), nor everywhere available (yet)

Faq:
- Is there also evidence for efficacy pharmacotherapy??
- Open studies, Placebo-controlled RCT’s, systematic reviews? Meta-analyses?
- How can this be translated into treatment algorithms and clinical guidelines?
Context is most important:

- Psychiatric management as prerequisite
- Psychotherapy whenever possible! First choice in guidelines.
- Medication only when necessary
- If so: invest in psycho-education
- Invest in relationship management: “Shared Decision Making”
- Start low, go slow!
- Avoid poly-pharmacy (no desperate cocktails!)
- Treat symptom (Axis I) disorders appropriately
- Discuss and register off-label medication
- Consider tapering off (effective as well as ineffective) medication
- Monitor compliance, side effects and suicidal ideation
- Invest in adequate multi disciplinary cooperation (split treatment)
Guidelines! What guidelines......??
This was the problem......in 2001 ???

- Frequent prescription psychotropic drugs
- High prevalence co-morbid disorders
- Immense polypharmacy in clinical practice
- Patients will abuse prescribed medication
- Unknown efficacy and effectiveness
- Behavioral dyscontrol and side effects
- Unknown mechanism of action
- Only one guideline (APA, 2001 & 2005)
- Psychiatrists and patients like drugs !?
APA practice guideline BPD 2001: Summary of recommendations

- **Psychiatric management as foundation** of all treatments
  (responding to crisis, monitoring safety, maintaining therapeutic framework)

- **Primary treatment** is (extended) **psychotherapy**......

- Complemented by **symptom-targeted pharmacotherapy**
  (adjunctive role for temporary diminution of symptoms)

- Patients will benefit most from a **combination** of these treatments.

- Good **collaboration** among treatment members and clarify of roles are essential

Theo Ingenhoven
symptom-targeted pharmacotherapy
Paul Soloff (1998)

- **Cognitive perceptual symptoms**: Suspiciousness, referential thinking, paranoid ideation, illusions, derealization, depersonalization, hallucination-like symptoms……..

- **Affective dysregulation**: Mood lability, rejection sensitivity, inappropriate intense anger, depressive “mood crashes”, outburst of temper……..

- **Impulsive-behavioral dyscontrol**: Impulsive aggression, self-mutilation, promiscuous sex, substance abuse, reckless spending……..
APA 2001 three algorithms

Cognitive perceptual symptoms

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Practice Guideline for the Treatment of Patients With Borderline Personality Disorder
Patient exhibits mood lability, rejection sensitivity inappropriate intense anger, depressive "mood crashes," or outbursts of temper.

Initial treatments: SSRI or related antidepressant.

Efficacy → Maintenance

Partial Efficacy → Switch

No Efficacy → Second SSRI or related antidepressant

Efficacy → Maintenance

Partial Efficacy → Add

No Efficacy → Add: Low-dose neuroleptic (for symptoms of anger), clonazepam (for symptoms of anxiety)

(If ineffective) Switch to MAOI

Efficacy → Maintenance

Partial Efficacy → Add

No Efficacy → Switch

Add: Lithium, carbamazepine, or valproate

APA, 2001

Affective dysregulation

Practice Guideline for the Treatment of Patients With Borderline Personality Disorder

American Psychiatric Association
Impulsive-behavioral dyscontrol
Where are we now......in 2018 ???

- Frequent prescriptions psychopharmaca in borderline patients
- High prevalence co-morbid disorders
- Polypharmacy in clinical practice
- Abuse prescribed medication
- More data on efficacy and effectiveness
- More knowledge on side effects
- Unknown mechanism of action
- About ten clinical guidelines !!
- Psychiatrists and patients still love drugs !!
More recent guidelines and algorithms ??

Australia 2013

Clinical Practice Guideline for the Management of Borderline Personality Disorder

Australian Government
National Health and Medical Research Council

Theo Ingenhoven
Dutch guidelines for diagnosis and treatment of adult patients with personality disorders
2008
Multidisciplinary Guideline Personality Disorders

Global conclusions & recommendations

**Diagnosis**
- Point of departure: DSM-IV Axis II diagnostic classification
- Clinical diagnostic process & specific assessment procedures

**Treatment**
- Psychotherapy whenever possible (first choice)
- Pharmacotherapy whenever necessary
- Special attention for comorbid Axis-I disorders

**Organization mental health care**
- Primary care and specialized health care
- Combine stepped-care & matched care
- Case-management & milieu
- Monitoring & empirical research

Theo Ingenhoven
Can borderline patients profit from pharmacotherapy?

and if……

and if so……

from what kind of medication borderline patients can profit?
Presumptions Dutch algorithms

- Some personality dimensions are mediated by dysregulation of neurotransmitter systems.
- Try to treat both symptoms and trait vulnerabilities
- Focus on specific symptom domains

- **Better a limited guideline than no guideline at all!**

- Use the best evidence available
- Include as much (additional) information as possible
- Weigh up the pros (efficacy) and cons (stigma; side-effects; costs)
- Tailor available scientific data into clinical wisdom
Dutch Guideline (2008)
pharmacotherapy algorithms

- Systematic review
- Meta-analysis
• **Treatment co-morbid disorders (Axis-I)**
  - Major depressive disorder
  - Bipolar disorder
  - Anxiety disorder and PTSD
  - Addictions
  - Eating disorders
  - ADHD/ADD in adults

• **Target symptom domains (within Axis-II)**
  - Cognitive-perceptual
  - Impulsive behavioral dyscontrol
  - Affective dysregulation

Use specific guideline (modified)?

New algorithms!
Effectiveness of Pharmacotherapy for Severe Personality Disorders: Meta-Analyses of Randomized Controlled Trials

Theo Ingenhoven et al

Journal of Clinical Psychiatry, 71, 14-25, 2010

- Published PC-RCT’s 1980 – 2007
- Borderline and/or Schizotypal PD
Outcome domains meta-analysis

All relevant compatible outcome variables (scales and subscales)
Classified into (sub)domains:

- Cognitive perceptual symptoms
- Impulsive behavioral dyscontrol
- Affective dysregulation
  - Depressed mood
  - Anxiety
  - Anger
  - Affect lability
- Global (social) functioning
- Severity personality disorder
Placebo effects in Borderline-Studies

- Placebo effect: up to 60%
- Not well estimated by doctors
- Nor by the patients
Aggregated placebo responses (1980-2012) in PC-RCTs with antipsychotics, antidepressants or mood stabilizers

<table>
<thead>
<tr>
<th>Outcome domain</th>
<th>Placebo: aggregated responses covering all PC-RCTs in BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (n)</td>
</tr>
<tr>
<td>Cognitive perceptual</td>
<td>13 (550)</td>
</tr>
<tr>
<td>Dissociation</td>
<td>19 (612)</td>
</tr>
<tr>
<td>Impulsivity/agression</td>
<td>17 (604)</td>
</tr>
<tr>
<td>Depression</td>
<td>12 (412)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>17 (612)</td>
</tr>
<tr>
<td>Mood shifts</td>
<td>5 (372)</td>
</tr>
<tr>
<td>Global functioning</td>
<td>13 (558)</td>
</tr>
<tr>
<td>BPD severity</td>
<td>8 (448)</td>
</tr>
</tbody>
</table>

Pre-post analyses
Placebo arms all RCTs

Highly significant
Large effect sizes

Moderate on:
- cogn-perceptual
- Impulsivity
- Anxiety/depression

Effect size = pooled Standardized Mean Difference = pooled Cohen’s d

**Bold** *= significant p≤0.05; **Bold** ** *= significant p≤0.01; **Bold**** *= significant p≤0.001

Qualification effect size: 0.20 = small; 0.50 = moderate; 0.80 = large
Efficacy ??

- Moderate to large placebo responses to compete with
- Open studies not helpful for efficacy
- Rely on placebo controlled RCT’s!
# Antipsychotics in BPD (2018)

<table>
<thead>
<tr>
<th>PC-RCT</th>
<th>Antipsychotic</th>
<th>Patients</th>
<th>Design</th>
<th>Symptom domain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cognitive-perceptual symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number, N (% drop out*)</td>
<td>Gender: In/out-patients</td>
<td>Duration weeks</td>
</tr>
<tr>
<td>Montgomery (1982)*</td>
<td>Flupentixol im</td>
<td>20 mg/4wks</td>
<td>m/v</td>
<td>In/out</td>
</tr>
<tr>
<td>Goldberg (1986)*</td>
<td>Thiothixene</td>
<td>8.7 mg/d</td>
<td>50 (48%)</td>
<td>m/v</td>
</tr>
<tr>
<td>Cowdry (1988)*</td>
<td>Trifluoperazine</td>
<td>7.8 mg/d</td>
<td>23 (57%)</td>
<td>v</td>
</tr>
<tr>
<td>Soloff (1989)</td>
<td>Haloperidol</td>
<td>4-16 mg/d</td>
<td>60 (7%)</td>
<td>m/v</td>
</tr>
<tr>
<td>Soloff (1993)</td>
<td>Haloperidol</td>
<td>4 mg/d</td>
<td>70 (17%)</td>
<td>m/v</td>
</tr>
<tr>
<td>Cornelius (1993)*</td>
<td>Haloperidol</td>
<td>&lt;6 mg/d</td>
<td>32 (25%)</td>
<td>m/v</td>
</tr>
<tr>
<td>Zanarini (2001)*</td>
<td>Olanzapine</td>
<td>5.3 mg/d</td>
<td>28 (50%)</td>
<td>v</td>
</tr>
<tr>
<td>Bogenschutz (2004)</td>
<td>Olanzapine</td>
<td>2.5-20 mg/d</td>
<td>40 (43%)</td>
<td>m/v</td>
</tr>
<tr>
<td>Soler (2005)</td>
<td>Olanzapine</td>
<td>5-20 mg/d</td>
<td>60 (30%)</td>
<td>m/v</td>
</tr>
<tr>
<td>Zanarini (2006)</td>
<td>Olanzapine</td>
<td>2.5 mg/d</td>
<td>303 (37%)</td>
<td>m/v</td>
</tr>
<tr>
<td>Zanarini (2006)</td>
<td>Olanzapine</td>
<td>5-10mg/d</td>
<td>298 (35%)</td>
<td>m/v</td>
</tr>
<tr>
<td>Nickel (2006)</td>
<td>Aripiprazol</td>
<td>15 mg/d</td>
<td>52 (10%)</td>
<td>m/v</td>
</tr>
<tr>
<td>Pascual (2008)</td>
<td>Ziprasidone</td>
<td>40-200 mg/d</td>
<td>60 (52%)</td>
<td>m/v</td>
</tr>
<tr>
<td>Schulz (2006, 2008)</td>
<td>Olanzapine</td>
<td>2.5-20 mg/d</td>
<td>314 (43%)</td>
<td>m/v</td>
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<tr>
<td>Linehan (2008)</td>
<td>Olanzapine</td>
<td>2.5-15mg/d</td>
<td>24 (33%)</td>
<td>v</td>
</tr>
<tr>
<td>vd Broek (2008)</td>
<td>Quetiapine</td>
<td>200-600 mg/d</td>
<td>24 (33%)</td>
<td>m/v</td>
</tr>
<tr>
<td>Black (2014)</td>
<td>Quetiapine</td>
<td>150/300 mg/d</td>
<td>95 (33%)</td>
<td>m/f</td>
</tr>
</tbody>
</table>

*Study not included in meta-analysis; †Drop-out rate not specified in publication. Symbols: ■ = Symptom domain in study statistical significant positive result, as compared with placebo condition; □ = Symptom domain in study not statistical significant positive result, as compared with placebo condition; ■□ = Symptom domain in study, with contradictory results within study.

17 studies
### Effect size = pooled Standardized Mean Difference = pooled Cohen’s d

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Qualification effect size: 0.20 = small; 0.50 = moderate; 0.80 = large

<table>
<thead>
<tr>
<th>Symptom domain:</th>
<th>Antipsychotics</th>
<th></th>
<th>Antidepressants</th>
<th></th>
<th>Mood stabilizers</th>
<th></th>
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<tr>
<td></td>
<td>N studies</td>
<td>effect size</td>
<td>N studies</td>
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<td>effect size</td>
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<tr>
<td>Cognitive-perceptual symptoms</td>
<td>11</td>
<td>0.32***</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Impulsive behavioral dyscontrol</td>
<td>12</td>
<td>0.21*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective dysregulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed mood</td>
<td>11</td>
<td>0.28*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>6</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger</td>
<td>9</td>
<td>0.39***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood swings</td>
<td>5</td>
<td>0.20**</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Global functioning</td>
<td>10</td>
<td>0.28*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity BPD</td>
<td>7</td>
<td>0.21**</td>
<td></td>
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**Theo Ingenhoven**
**Meta-analysis PC-RCTs 1980 - 2018**

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| Symptom domain: | Antipsychotics | | Antidepressants | | Mood stabilizers | |
| --- | --- | --- | --- | --- | --- |
| | N studies | effect size | N studies | effect size | N studies | effect size |
| Cognitive-perceptual symptoms | 11 | **0.32*** | | | | |
| Impulsive behavioral dyscontrol | 12 | **0.21*** | | | | |
| Affective dysregulation | | | | | | |
| Depressed mood | 11 | **0.28*** | | | | |
| Anxiety | 6 | 0.23 | | | | |
| Anger | 9 | **0.39*** | | | | |
| Mood swings | 5 | **0.20** | | | | |
| Global functioning | 10 | **0.28*** | | | | |
| Severity BPD | 7 | **0.21** | | | | |

Active n=704  
Placebo n= 522
SSRI’s in Borderline PS ??

APA (2001; no adjustments in 2005)

SSRI first and second choice in the treatment algorithms of behavioral dyscontrol and affective dysregulation.

Practice guideline for treatment of patients with borderline personality disorder
### Antidepressants in BPD (2018)

<table>
<thead>
<tr>
<th>First author (year publication)</th>
<th>Active medication</th>
<th>Dose</th>
<th>Number, N (%)</th>
<th>Setting: gender</th>
<th>Duration weeks</th>
<th>Cognitive-perceptual symptoms</th>
<th>Impulsive-behavioral dyscontrol</th>
<th>Affective dysregulation</th>
<th>Global functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montgomery (1982)</td>
<td>Mianserine</td>
<td>30 mg</td>
<td>38 (ns)</td>
<td>m/f</td>
<td>24</td>
<td>□</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cowdry (1988)</td>
<td>Tranylcypromine</td>
<td>40 mg</td>
<td>25 (11%)</td>
<td>f</td>
<td>6</td>
<td>■□</td>
<td>■</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Soloff (1989)</td>
<td>Amitriptyline</td>
<td>100-175 mg</td>
<td>59 (2%)</td>
<td>m/f</td>
<td>In</td>
<td>6</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Links (1990)b</td>
<td>Desipramine</td>
<td>163 mg</td>
<td>25 (8%)</td>
<td>m/f</td>
<td>In</td>
<td>6</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Soloff (1993)</td>
<td>Phelazine</td>
<td>60 mg</td>
<td>72 (10%)</td>
<td>m/f</td>
<td>In</td>
<td>5</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Cornelius (1993)b</td>
<td>Phelazine</td>
<td>≤90 mg</td>
<td>40 (9%)</td>
<td>m/f</td>
<td>Out</td>
<td>16</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Salzman (1995)</td>
<td>Fluoxetine</td>
<td>40 mg</td>
<td>27 (5%)</td>
<td>m/f</td>
<td>Out</td>
<td>12</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Markovitz (1995)</td>
<td>Fluoxetine</td>
<td>80 mg</td>
<td>17 (3%)</td>
<td>m/f</td>
<td>In/out</td>
<td>14</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Coccaro (1997)</td>
<td>Fluoxetine</td>
<td>20-60 mg</td>
<td>40 (14%)</td>
<td>m/f</td>
<td>Out</td>
<td>13</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Rinne (2002)</td>
<td>Fluvoxamine</td>
<td>150 mg</td>
<td>38 (3%)</td>
<td>f</td>
<td>Out</td>
<td>6</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Simpson (2004)</td>
<td>Fluoxetine</td>
<td>Max 40 mg</td>
<td>25 (5%)</td>
<td>m/f</td>
<td>In/out</td>
<td>12</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

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11 studies
## Meta-analysis PC-RCTs 1980 - 2018

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<td>effect size</td>
<td>N studies</td>
</tr>
<tr>
<td>Cognitive-perceptual symptoms</td>
<td>11</td>
<td><strong>0.32</strong>*</td>
<td>3</td>
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<tr>
<td>Impulsive behavioral dyscontrol</td>
<td>12</td>
<td><strong>0.21</strong>*</td>
<td>5</td>
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<tr>
<td>Affective dysregulation</td>
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</tr>
<tr>
<td>Anger</td>
<td>9</td>
<td><strong>0.39</strong>*</td>
<td>4</td>
</tr>
<tr>
<td>Mood swings</td>
<td>5</td>
<td><strong>0.20</strong>*</td>
<td>1</td>
</tr>
<tr>
<td>Global functioning</td>
<td>10</td>
<td><strong>0.28</strong>*</td>
<td>4</td>
</tr>
<tr>
<td>Severity BPD</td>
<td>7</td>
<td><strong>0.21</strong>*</td>
<td>1</td>
</tr>
</tbody>
</table>

Effect size = pooled Standardized Mean Difference = pooled Cohen’s d
**Bold***= significant p≤0.05; **Bold****= significant p≤0.01; **Bold***** = significant p≤0.001

Qualification effect size: 0.20 = small; 0.50 = moderate; 0.80 = large
# Moodstabilizers in BPD (2018)

<table>
<thead>
<tr>
<th>PC-RCT</th>
<th>Moodstabilizer</th>
<th>Patients</th>
<th>Design</th>
<th>Symptom domain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cognitive-perceptual symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number, N (%)</td>
<td>Gender: m/f</td>
<td>Setting: In/out-patients</td>
</tr>
<tr>
<td>Cowdry (1988)</td>
<td>Carbamazepine</td>
<td>820 mg</td>
<td>28 (13)</td>
<td>f</td>
</tr>
<tr>
<td>Links (1990)b</td>
<td>Lithium</td>
<td>986 mg</td>
<td>24 (8)</td>
<td>m/f</td>
</tr>
<tr>
<td>De la Fuente (1994)</td>
<td>Carbamazepine</td>
<td>Blood level</td>
<td>20 (2)</td>
<td>m/f</td>
</tr>
<tr>
<td>Hollander (2001)</td>
<td>Valproaat</td>
<td>Blood level</td>
<td>16 (10)</td>
<td>m/f</td>
</tr>
<tr>
<td>Frankenburg (2002)</td>
<td>Valproaat</td>
<td>500 mg</td>
<td>30 (19)</td>
<td>f</td>
</tr>
<tr>
<td>Hollander (2003)b</td>
<td>Valproaat</td>
<td>Blood level</td>
<td>91 (8)</td>
<td>m/f</td>
</tr>
<tr>
<td>Nickel (2004)</td>
<td>Topiramaat</td>
<td>50-250 mg</td>
<td>31 (2)</td>
<td>f</td>
</tr>
<tr>
<td>Trutt (2005)</td>
<td>Lamotrigine</td>
<td>50-200 mg</td>
<td>27 (3)</td>
<td>f</td>
</tr>
<tr>
<td>Nickel (2005)</td>
<td>Topiramaat</td>
<td>50-250 mg</td>
<td>44 (2)</td>
<td>m</td>
</tr>
<tr>
<td>Loew (2006)</td>
<td>Topiramaat</td>
<td>25-200 mg</td>
<td>56 (4)</td>
<td>f</td>
</tr>
<tr>
<td>Reich (2009)</td>
<td>Lamotrigine</td>
<td>25-225mg</td>
<td>28(39)</td>
<td>m/f</td>
</tr>
<tr>
<td>Moen (2012)</td>
<td>Valproaat ERc</td>
<td>1000-2000mg</td>
<td>15(6)</td>
<td>m/f</td>
</tr>
<tr>
<td>Crawford (2018)</td>
<td>Lamotrigine</td>
<td>100-200 mg</td>
<td>273 (29)</td>
<td>m/f</td>
</tr>
</tbody>
</table>

bStudy not included in meta-analysis; cDrop-out rate not specified in publication. Symbols: ■ = Symptom domain in study statistical significant positive result, as compared with placebo condition; □ = Symptom domain in study not statistical significant positive result, as compared with placebo condition; ■□ = Symptom domain in study, with contradictory results within study.

13 studies
PC-RCT Lamotrigine

LABILE STUDY: Crawford et al. (2018)
Lamotrigine and borderline personality disorder: Investigating long-term effects
American Journal of Psychiatry
BPD adults, without bipolar disorder, without mood stabilizer
N=137 TAU + Lamotrigine 200 mg/day
N=139 TAU + Placebo

Severity BPD: Zanarini scale + subscales
Depression: Beck Depression Inventory
Self Harm Inventory
Adherence
Social functioning
Quality of life
FIGURE 2. Change in Score on the Zanarini Rating Scale for Borderline Personality Disorder at 12, 24, and 52 Weeks in a Placebo-Controlled Study of Lamotrigine for People With Borderline Personality Disorder

The Clinical Effectiveness and Cost-Effectiveness of Lamotrigine in Borderline Personality Disorder: A Randomized Placebo-Controlled Trial

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The Clinical Effectiveness and Cost-Effectiveness of Lamotrigine in Borderline Personality Disorder: A Randomized Placebo-Controlled Trial

## Meta-analysis PC-RCTs 1980 - 2018

Effect size = pooled Standardized Mean Difference = pooled Cohen’s d

**Bold** *= significant p≤0.05; **Bold** **= significant p≤0.01; **Bold** *** = significant p≤0.001

Qualification effect size: 0.20 = small; 0.50 = moderate; 0.80 = large

<table>
<thead>
<tr>
<th>Symptom domain:</th>
<th>Antipsychotics</th>
<th>Antidepressants</th>
<th>Mood stabilizers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N studies</td>
<td>effect size</td>
<td>N studies</td>
</tr>
<tr>
<td>Cognitive-perceptual symptoms</td>
<td>11</td>
<td><strong>0.32</strong>*</td>
<td>3</td>
</tr>
<tr>
<td>Impulsive behavioral dyscontrol</td>
<td>12</td>
<td><strong>0.21</strong>*</td>
<td>5</td>
</tr>
<tr>
<td>Affective dysregulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed mood</td>
<td>11</td>
<td><strong>0.28</strong>*</td>
<td>6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6</td>
<td>0.23</td>
<td>5</td>
</tr>
<tr>
<td>Anger</td>
<td>9</td>
<td><strong>0.39</strong>***</td>
<td>4</td>
</tr>
<tr>
<td>Mood swings</td>
<td>5</td>
<td><strong>0.20</strong>**</td>
<td>1</td>
</tr>
<tr>
<td>Global functioning</td>
<td>10</td>
<td><strong>0.28</strong>*</td>
<td>4</td>
</tr>
<tr>
<td>Severity BPD</td>
<td>7</td>
<td><strong>0.21</strong>**</td>
<td>1</td>
</tr>
</tbody>
</table>

Theo Ingenhoven
1. Classical and atypical antipsychotics **both** effective on cognitive-perceptual symptoms and anger (but differ in costs and side effects)

2. Moodstabilizers seems **most** effective on affective dysregulation and impulsive-behavioral dyscontrol

3. Moodstabilizers **outperform** SSRIs on affective dysregulation and impulsivity

4. Discourage addition strategies and polypharmacy
Atypical neuroleptics
- Cognitive perceptual symptoms
- Impulsive behavioral dyscontrol & anger

SSRI’s
- Emotional dysregulation (depressive mood, anxiety & mood swings)

Moodstabilizers
- As second-line treatment for impulsive or aggressive behavior
NICE (2009)

National Institute for Health and Clinical Excellence
- Borderline PD
- Antisocial PD
The role of drug treatment:

“Drug treatment should not be used specifically for BPD, nor for individual symptoms nor for behavior associated with BPD.”
Because

• Virtually all the trials were funded by the pharmaceutical industry
• The smallest ones were the most positive
• We suspected fraud in many trials
• There was no good evidence of replication
• We suspected a strong degree of publication bias
• The adverse effects of drug treatment were rarely considered
NICE clinical guideline (2009)
Borderline personality disorder

- **No** antipsychotics for medium to long term treatment
- **Drug treatment only for** comorbid conditions like depression, PTSD or anxiety disorder (follow specific NICE clinical guidelines)
- **In crisis:** short term sedative medication (< 1 week)
  i.e. sedative antihistamine
- **Stop unnecessary drug treatment**
More recent guidelines and algorithms ??

Australia 2013

Clinical Practice Guideline for the Management of Borderline Personality Disorder

Australian Government National Health and Medical Research Council

About the Guideline

- NHMRC Guideline - funded by Federal Department of Health and Ageing
- First Australian guideline for BPD
- Adapted from the 2009 NICE Guideline on BPD
- Advised by a multi-disciplinary guideline development committee
- Aimed at health professionals managing patients with BPD
- Released in March 2013
Is NHMRC that different to NICE?

**NICE advocates for total abstinence**

**NHMRC advocates for harm minimisation**
More recent guidelines and algorithms ??

Denmark 2015

National klinisk retningslinje for behandling af emotional ustabil personlighedsstruktur, borderline type

Sundhedsstyrelsen

Danish Health and Medicines Authority
Danish guideline BPD 2015

- Systematic review including all peer reviewed RCT’s
  - Antipsychotics 11 RCT’s
  - Antidepressants 8 RCT’s
  - Mood stabilizers 8 RCT’s
- Level of evidence (Grade) is (very) low
- Most important outcome measures:
  - Borderline severity
  - Social functioning
  - Quality of life
  - Serious adverse events
- Weak /conditional recommendation against
Danish guideline BPD 2015

- Systematic review including all peer reviewed RCT’s
  - Antipsychotics 11 RCT’s
  - Antidepressants 8 RCT’s
  - Mood stabilizers 8 RCT’s

- Level of evidence (Grade) is low to moderate
- Most important outcome measures:
  - Borderline severity
  - Social functioning
  - Quality of life
  - Serious adverse events

Recommendations: Antipsychotics, antidepressants or mood stabilizers should only be used in the treatment of BPD *upon due consideration*.
In conclusion:

International guidelines advocate for:
- **APA:** Add-on strategies (including lithium, MAOI, Clozapine)
- **Dutch/German:** Symptom-targeted treatment algorithms (monotherapy)
- **NICE:** total abstinence
- **Australian:** harm minimization
- **Danish:** only after due consideration
In conclusion:

International guidelines advocate for:

- APA: Add-on strategies (including lithium, MAOI, Clozapine)
- Dutch/German: Symptom-targeted treatment algorithms (monotherapy)
- NICE: total abstinence
- Australian: harm minimization
- Danish: only after due consideration

ESSPD ??
One European guideline?
In conclusion:

- Where results of RCT’s and meta-analyses slowly converge
- North American, European and Australian guidelines and treatment algorithms still diverge
- First: do no harm!
- Whenever pharmacotherapy in BPD is indicated, it should be guided by

  Symptom-targeted Treatment Algorithms
Recommended book chapter

Kenneth Silk et al 2016
Chapter pharmacotherapy in:

Thank you for your attention
1. Cognitive-perceptual symptoms


1. Classical antipsychotic, low dose
2. Classical antipsychotic, raise dose
3. Atypical antipsychotic

Recommendations  
Ingenhoven & Rinne (2007)

(pseudo)psychotic symptoms
1. Classical or atypical antipsychotic, low dose
2. Raise dose

Dissociation
   No recommendation

Avoid
   benzodiazepines (high dose)
   tricyclic antidepressants
   high dose topiramate
   polypharmacy
2. Impulsive-behavioral dyscontrol


1. SSRIs
2. Add classical antipsychotic
3. Carbamazepine, Valproate or Lithium
4. Atypical antipsychotic

**Recommendations**
**Ingenhoven & Rinne** (2007)

1. Topiramate
2. **Male**: SSRI or valproate  
   **Female**: Valproate
3. Antipsychotic  
   (classical or atypical)

**Avoid**
benzodiazepines (high dose)  
tricyclic antidepressants  
polypharmacy
3. affective dysregulatie


1. SSRI or related antidepressant (2X)
2. **Anxiety:**
   - add benzodiazepine
3. **Anger:**
   - add antipsychotic (low dose)
4. Mao-inhibitor
5. Lithium, Carbamazepine or Valproate

Recommendations
Ingenhoven & Rinne (2007)

**Differentiate sub-domains:**
- Affective lability
  - SSRI ?? Valproate ??
- “Depressed mood”
  - atypical antipsychotic
- Anxiety
  - antipsychotic (classical or atypical)
- Anger, hostility, irritability
  1. topiramate, valproate (lamotrigine)
  2. antipsychotic (classical or atypical)