Pharmacotherapy for personality disorders

Birgit Völlm
Reader & Clinical Associate Professor in Forensic Psychiatry
University of Nottingham
Rampton Hospital
Outline

• Prescribing in borderline PD
• Treatment targets
• Rationale for pharmacological treatment
• Cochrane review Pharmacological interventions in BPD
• NICE guidance – discrepancies
• (Antisocial PD)
• Discussion
  – Discrepancies Cochrane reviews / NICE guidance / own practice
  – ‘Success stories’ – why?
About you

• Professional background
• Expectations of session
• Own prescribing practice
Helpful drugs in borderline PD

The most helpful pharmacological intervention in borderline PD is

- SSRIs
- Other antidepressant
- Olanzapine
- Sodium Valproate
- Other mood stabiliser
- Haloperidol
- Other antipsychotic
Prescribing in borderline PD

Polypharmacy (Zanarini et al., 2004), 6 yrs follow-up
- About 80% on medication
  - 50% 2 or more drugs
  - 40% 3 or more
  - 19% 4 or more
  - 11% 5 or more

UK community prescribing PD (Baker-Glenn et al., 2010)
- 81% prescribed at least one psychotropic medication
  - 39% one
  - 23% two
  - 13% three
  - 3% four
  - 1% five

Drugs used (Bender et al., 2001)
- 61% antidepressant, 35% anxiolytic, 27% mood stabiliser, 10% antipsychotics
Co-morbidity

• **Axis I** – **Axis II** (lifetime prevalence total ~ 90%; Zimmermann & Mattia, 1999)
  – Mood disorders
  – Anxiety disorders
  – Substance related disorders
  – PTSD
  – Eating disorders
• **Axis II** – **Axis II**
  – ‘Co-morbid’ personality disorders
• **Axis II** – **Axis III**
• 60-70% suicide attempts
• 10% suicide
PD Prescribing in forensic care

• 79% of PD patients on medication
• Co-morbidity high but
• 65% prescribed specifically for PD
• Most commonly used drugs
  – 46% mood stabilisers (Valproate preparations)
  – 45% SGA (Quetiapine)
  – 25% SSRIs
  – 23% clozapine
• Reasons for prescribing: Domain specific
Treatment targets

- Axis I co-morbidity
- Treatment of the personality disorder
- Treatment of specific symptoms
- Psychosocial functioning
- Crisis
- Enables better engagement in other therapies
- Helplessness – nothing else available
Rationale for pharmacological treatment of borderline PD

- Continuum between PD and mental illness (Atre-Vaidya 1999)
  - Related symptoms share common pathophysiology
- Certain dimensions of personality are mediated by specific neurotransmitters
- Neurotransmitter abnormalities in BPD
  - Inverse correlation between impulsivity and serotonin levels
Pharmacological interventions for borderline personality disorder (Review)

## Cochrane Collaboration reviews

<table>
<thead>
<tr>
<th>PD</th>
<th>Pharmacological</th>
<th>Psychological</th>
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<tbody>
<tr>
<td>Paranoid</td>
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<td>Schizoid</td>
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<td>Data extraction</td>
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<td>Narcissistic</td>
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<td>Obsessive-compulsive</td>
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<tr>
<td>Dependent</td>
<td>Data extraction</td>
<td>Data extraction</td>
</tr>
<tr>
<td>Avoidant</td>
<td>Data extraction</td>
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</tbody>
</table>
Methods

Search strategy
• Cochrane Developmental, Psychosocial and Learning Problems Group maximally sensitive search strategy (electronic databases, study registers)
• Survey of relevant journals (J Pers Disorders, Am J Psychiatry, J Clin Psychology, etc.)
• Tracking of cross-references and review articles
• E-mail survey among researchers
• No language restrictions

Study selection
• References independently appraised and selected by two reviewers (JS, BV) according to inclusion criteria

Analysis
• Quality appraisal/risk of bias assessment and data extraction by two reviewers independently
• Computation of effect sizes according to standards of the Cochrane Collaboration, post treatment group differences
Inclusion criteria

**Participants**
Adult BPD patients

**Interventions**
RCTs of any medication delivered continuously to ameliorate BPD or associated psychopathology

**Comparisons**
Active drug vs. placebo
(Active drug vs. comparison [i.e., single or combined] treatment)

**Outcomes**
1. BPD severity
2. BPD core pathology
3. Associated psychopathology
4. Tolerability and safety
Results from searches

13972 references

removal of duplicates

10249 screened by title and abstract

removal of references not meeting inclusion criteria

489 screened by looking at the full article text

removal of references not meeting inclusion criteria

57 references included, referring to 28 RCTs
Publication years

Pharma studies
Summary of study characteristics

- 28 studies
- 14 USA, 12 Western Europe, 2 multi-center
- Total data on 1742 participants, study size 16 – 314
- Mean duration 84 days (range 32 days to 24 weeks)
- Mostly female out-patient samples
- Age range 21.7 to 38.6
- Mild to moderate symptoms: GAF 40 - 70
- Most studies excluded serious mental illness
Drug classes used

Type of drug

- Typical AP
- Atypical AP
- SSRIs
- Other AD
- Mood stabilisers
- Omega fatty acids
### Placebo controlled comparisons

<table>
<thead>
<tr>
<th><strong>first-generation antipsychotics (FGAs)</strong></th>
<th><strong>mood stabilisers (MS)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>haloperidol (N=2)</td>
<td>carbamazepine (N=1)</td>
</tr>
<tr>
<td>thiothixene (N=1)</td>
<td>valproate semisodium (N=2)</td>
</tr>
<tr>
<td>flupenthixol decanoate (N=1)</td>
<td>lamotrigine (N=2)</td>
</tr>
<tr>
<td></td>
<td>topiramate (N=3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>second-generation antipsychotics (SGAs)</strong></th>
<th><strong>antidepressants (AD)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>aripiprazole (N=1)</td>
<td>amitriptyline (N=1)</td>
</tr>
<tr>
<td>olanzapine (N=6)</td>
<td>fluoxetine (N=2)</td>
</tr>
<tr>
<td>ziprasidone (N=1)</td>
<td>fluvoxamine (N=1)</td>
</tr>
<tr>
<td></td>
<td>phenelzine sulfate (N=1)</td>
</tr>
<tr>
<td></td>
<td>mianserin (N=1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>dietary supplementation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>omega-3 fatty acids (N=2)</td>
</tr>
</tbody>
</table>
# First-generation antipsychotics vs. placebo

Summary of significant findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Flupenthixol (1 RCT)</th>
<th>Haloperidol (2 RCTs)</th>
<th>Thiothixene (1 RCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD severity</td>
<td>-</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>BPD pathology</td>
<td>self-harm RR 0.49</td>
<td>anger (n=2) SMD -0.46</td>
<td>n.s.</td>
</tr>
<tr>
<td>Associated psychopathology</td>
<td>-</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Attrition</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
### Second-generation antipsychotics vs. placebo

#### Summary of significant findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Olanzapine (total 6 RCTs)</th>
<th>Aripiprazole (1 RCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD total severity</td>
<td>n.s.</td>
<td>-</td>
</tr>
<tr>
<td>BPD pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>affect. instability (n=3)</td>
<td>MCD -0.16</td>
<td></td>
</tr>
<tr>
<td>suicidality (n=2)</td>
<td>MCD  0.29</td>
<td>interspers. problems</td>
</tr>
<tr>
<td>anger (n=3)</td>
<td>MCD -0.27</td>
<td>impulsivity</td>
</tr>
<tr>
<td>psychotic symptoms</td>
<td>MCD -0.18</td>
<td>anger</td>
</tr>
<tr>
<td></td>
<td></td>
<td>psychot. symptoms</td>
</tr>
<tr>
<td>Associated psychopathology</td>
<td>anxiety</td>
<td>MCD -0.22</td>
</tr>
<tr>
<td>depression</td>
<td></td>
<td>SMD -1.25</td>
</tr>
<tr>
<td>anxiety</td>
<td></td>
<td>SMD -0.73</td>
</tr>
<tr>
<td>general psychopath.</td>
<td></td>
<td>SMD -1.27</td>
</tr>
<tr>
<td>Attrition</td>
<td>n.s.</td>
<td>-</td>
</tr>
</tbody>
</table>

No sig. findings from RCTs for Ziprasidone (1 RCT available)
Mood stabilisers vs. placebo
Summary of significant findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lamotrigine (2 RCTs)</th>
<th>Topiramate (3 RCTs)</th>
<th>Valproate semisodium (2 RCTs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD severity</td>
<td>n.s.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BPD pathol. impulsiv.</td>
<td>SMD -1.62 MCD -1.41</td>
<td>SMD -0.91</td>
<td>interpers. probl. SMD -1.04</td>
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<tr>
<td>anger (n=2)</td>
<td>SMD -1.69</td>
<td>SMD -3.36</td>
<td>SMD -1.83</td>
</tr>
<tr>
<td>Associated psychopath.</td>
<td>-</td>
<td>anxiety general psych.</td>
<td>depression (n=2) SMD -0.66</td>
</tr>
<tr>
<td>Attrition</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

No sig. findings from RCTs for Carbamazepine (1 RCT available)
Antidepressants vs. placebo
Summary of significant findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TCA: Amitriptyline (1 RCT)</th>
<th>TCA: Mianserin (1 RCT)</th>
<th>MAOI: Phenelzine (1 RCT)</th>
<th>SSRI: Fluoxetine (2 RCTs)</th>
<th>SSRI: Fluvoxamine (1 RCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD severity</td>
<td>-</td>
<td>-</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPD pathology</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Associated psychopathol.</td>
<td>depression SMD -0.59</td>
<td>-</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Attrition</td>
<td>n.s.</td>
<td>-</td>
<td>n.s.</td>
<td>n.s.</td>
<td>-</td>
</tr>
</tbody>
</table>
## Miscellaneous vs. placebo

### Summary of significant findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Omega-3-fatty acids (2 RCTs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD severity</td>
<td>-</td>
</tr>
<tr>
<td>BPD pathology</td>
<td><strong>suididality</strong> RR 0.52-0.59</td>
</tr>
<tr>
<td>associated psychopath.</td>
<td><strong>depression</strong> RR 0.48</td>
</tr>
<tr>
<td>attrition</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
Summary of findings

• Limited evidence base for prescribing
• No effect on overall severity of illness
• No effect of antidepressants on BPD symptomatology
• Most promising results for second generation AP (olanzapine, aripiprazole) and mood stabilisers (valproate, lamotrigine, topiramate)
Domain specific prescribing (Soloff)

- **Cognitive-perceptual**
  - Transient psychosis, paranoid
  - Overvalued ideas
  - Unusual perceptual experiences
  - Identity disturbance
  - Body image disturbance

- **Affective disturbance**
  - Affective instability
  - Increased mood reactivity
  - Anger, tension, panic
  - Dysphoria
  - Emptiness
  - Depression, anxiety

- **Impulsive-behavioural**
  - Impulsivity
  - Aggression
  - Self-harm
  - Suicidality

- **Interpersonal**
  - Efforts to avoid abandonment
  - Unstable relationships
Drug effects on specific symptoms

Some support for domain specific prescribing

- **Cognitive symptoms**: Aripiprazole, Olanzapine
- **Affective disturbance**:
  - Affective instability: Olanzapine
  - Anger: Haloperidol, Aripiprazole, Olanzapine, Valproate, Lamotrigine, Topiramate
- **Suicidal ideation**: Omega fatty acids; worsening with Olanzapine?
- **Suicidal behaviour**: Flupenthixol; worsening with Olanzapine?
- **Impulsivity**: Aripiprazole, Lamotrigine, Topiramate
- **Interpersonal symptoms**: Aripiprazole, Semisodium Valproate, Topiramate
- **No effect**: avoidance of abandonment, identify disturbance, chronic feelings of emptiness, dissociative symptoms, attrition
Limitations

• Samples mainly female, out-patients with mild to moderate BPD severity
• Exclusion of co-morbidity and problematic behaviours
• Short-term studies
• Most findings only supported by limited number of small trials
• Only for olanzapine moderate level of evidence for affective instability, anger and stress-related psychotic symptoms
People with BPD (or ASPD) should not be excluded from any health or social care service because of their diagnosis or their behaviour.
NICE guidance borderline PD

• Drug treatment should not be used for borderline personality disorder or for the individual symptoms or behaviour associated with the disorder (for example, repeated self-harm, marked emotional instability, risk-taking behaviour and transient psychotic symptoms)

• Review those currently prescribed medication with a view of reducing and stopping unnecessary drug treatment

• Drug treatment may be considered for co-morbid conditions

• Short-term management
<table>
<thead>
<tr>
<th>Drug</th>
<th>Group</th>
<th>Effect on</th>
<th>No effect on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin 300 mg / d</td>
<td>Male prisoners with recurrent aggressive behaviour</td>
<td>Frequency/intensity aggression (impulsive subgroup only)</td>
<td>Adverse events Hostility</td>
</tr>
<tr>
<td>(Barratt, 1997)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Desipramine 250 - 300 mg / d</td>
<td>OP, male, cocaine dependency, on methadone</td>
<td>Employment income (favours placebo group)</td>
<td>Illegal acts Social function Abstinence, drug use, craving, drug screens Employment Depression</td>
</tr>
<tr>
<td>(Arndt, 1994)</td>
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<tr>
<td>Desipramine 150 mg/ d</td>
<td>IP, opioid and cocaine dependency, on methadone</td>
<td>(No statistics on drug related measures)</td>
<td>Leaving study early</td>
</tr>
<tr>
<td>(Leal, 1994)</td>
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<tr>
<td>Nortryptiline 25 – 75 mg / d</td>
<td>Men with alcohol dependency and co-morbidity</td>
<td>Number drinking days, dependency index Beck’s anxiety scale</td>
<td>Leaving study early Glob al function Craving, alcohol abuse severity, abstinence SCL anxiety, depression</td>
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<td>(Powell, 1995)</td>
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<tr>
<td>Bromocriptine 15 / d</td>
<td>Men with alcohol dependency and co-morbidity</td>
<td>Beck’s anxiety scale</td>
<td>Leaving study early Global function Drinking days, craving, alcohol abuse severity, abstinence SCL anxiety, depression</td>
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<td>Amantadine 300 mg/ d</td>
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<td>(Leal, 1994)</td>
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</table>
Own questions and concerns

• How does your practice differ from the guidance
• Success stories – why were they successes?