Mifepristone (RU-486): Do You Believe in a Seven Day Choice for Psychotic Depression?

Pharmacotherapy Conference
February 10, 2012

Morgan C. Snyder, Pharm.D.
PGY2 Psychiatric Pharmacy Resident
The University of Texas at Austin College of Pharmacy

LEARNING OBJECTIVES:

- Discuss the clinical features and diagnostic criteria of Major Depressive Disorder (MDD) with Psychotic Features (Psychotic Major Depression, PMD)
- Review the pathophysiology of PMD with emphasis on the corticosteroid/dopamine hypothesis for psychotic depression
- Describe current evidence-based treatment options for PMD and issues with available options
- Discuss the proposed mechanism of mifepristone (RU-486) in the treatment of PMD
- Evaluate current literature assessing the efficacy and safety of mifepristone for treatment of PMD
- Formulate evidence-based conclusions regarding the role of mifepristone in the treatment of PMD
Major Depressive Disorder with Psychotic Features (Psychotic Major Depression, PMD)

I. EPIDEMIOLOGY

a. **Major Depressive Disorder (MDD):**
   i. National Comorbidity Survey Replication (NCS-R) study: lifetime prevalence among adults of 16.2%, with 12 month prevalence of 6.6%1

b. **Psychotic Major Depression (PMD):**
   i. Reported prevalence between 14 and 25% of MDD2-4 or 0.4-0.6% lifetime prevalence2,5

c. **Risk Factors:**
   i. MDD:1
      1. Female sex
      2. Middle-aged
      3. Never or previously married
      4. Low income
      5. Disabled
   ii. Patients with MDD may be more likely to have psychotic features if:3,7-8
      1. Feelings of worthlessness or guilt
      2. Past history of delusions
      3. Family history of bipolar disorder or schizophrenia
      4. Recurrent episodes of depression
      5. Longer duration of current depressive episode
      6. Increased severity of depression

II. COURSE OF ILLNESS

a. **Average Age of Onset:**
   i. MDD: Late 20s6
   ii. PMD: Inconsistent findings regarding difference between psychotic & nonpsychotic depression in age of onset2

b. **Duration of Illness:**
   i. PMD may be associated with a more chronic course of depression4, as well as longer duration of episodes and increased likelihood of recurrence5
   ii. However, initial diagnosis of PMD may change later in the course of psychiatric illness
      • Potential confusion with bipolar disorder, schizoaffective disorder, early schizophrenia, depression with concomitant substance use, PTSD, or dementia
      • Course and history of depressive and psychotic symptoms are key to making an appropriate diagnosis5

c. **Severity of Illness:**
   i. 2 fold greater risk of death vs. patients with severe, nonpsychotic MDD9
   ii. May be associated with more frequent hospitalizations, higher risk of suicide & greater disability than other forms of depression4

III. DSM-IV-TR DIAGNOSTIC CRITERIA10

a. **Major Depressive Episode:**
   i. 5 or more of the following for > 2 weeks which cause significant impairment in social/occupational functioning:
      1. Depressed mood*
      2. Diminished interest or pleasure in activities*
      3. Significant change in weight or appetite
      4. Insomnia or hypersomnia
      5. Psychomotor agitation or retardation
      6. Fatigue or loss of energy
      7. Feelings of worthlessness or excessive/inappropriate guilt
      8. Diminished ability to think or concentrate, or indecisiveness
      9. Suicidal ideation or suicide attempt
         *One of these two symptoms must be present
   ii. Symptoms are not accounted for by a substance, general medical condition or bereavement and do not meet criteria for a mixed episode
b. **MDD with Psychotic Features:**
   i. Major depressive episode + delusions/hallucinations
   ii. If possible, specify whether psychotic features are:
      1. **Mood-congruent:** content consistent with typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment
      2. **Mood-incongruent:** content does not involve typical depressive themes (may include persecutory delusions, thought insertion, thought broadcasting, or delusions of control)

### IV. PATHOPHYSIOLOGY

a. **Corticosteroid/Dopamine Hypothesis for Psychotic Depression:**
   i. Pronounced increases in hypothalamic-pituitary-adrenal (HPA) axis activity and downregulation of negative feedback
      1. Approximately 45 to 60% of patients with MDD have neuroendocrine abnormality, including cortisol hypersecretion
      2. HPA axis is reported to be more severely disordered in PMD vs. MDD
         a. Meta-analysis (n=1000): increased rates of nonsuppression on dexamethasone suppression tests in patients with psychotic (64%) vs. nonpsychotic (41%) depression
         b. Significant elevation in 24-hour urinary free cortisol levels and plasma ACTH observed in patients with PMD
   ii. Increased levels of cortisol in PMD can overload the stress response mechanism
   iii. Glucocorticoids increase dopamine activity in a variety of tissues, especially mesolimbic dopamine systems
      1. According to Schatzberg and colleagues, this may explain the development of psychosis in the context of a depressive episode
   iv. Glucocorticoid administration may cause cognitive deficits that mirror impairments in PMD

![Figure 1. Normal HPA Axis Function (left) versus HPA Dysfunction in Depression (right)](image-url)
V. CURRENT TREATMENT RECOMMENDATIONS

a. APA-Recommended First-Line Treatment Options:
   i. Electroconvulsive therapy
   ii. Pharmacotherapy
      1. Typically responds better to combination of an antipsychotic (AP) and an antidepressant (AD) medication
      2. Some research has shown comparable responses for AD or AP monotherapy
      3. Lithium augmentation is an option if no response to combination treatment

b. Electroconvulsive Therapy (ECT):
   i. Produces acute rises in cortisol & is thought to result in re-regulation of the HPA axis

Table 1. ECT for MDD with Psychotic Features

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Potential Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation within 5 days of admission shortens length of stay &amp; reduces treatment costs</td>
<td>Associated with longer length of stay if not initiated rapidly</td>
</tr>
<tr>
<td>Meta-analysis (44 studies): Trend for ECT to be superior to combination AP/AD or TCA monotherapy (no head to head comparisons)</td>
<td>Minority ethnic groups &amp; patients with low income or living in rural areas are less likely to receive ECT</td>
</tr>
<tr>
<td>ECT has been demonstrated to be effective acutely</td>
<td>Pharmacotherapy is still necessary to avoid relapse &amp; subsequent hospitalization</td>
</tr>
<tr>
<td></td>
<td>Cognitive adverse effects of ECT in a patient population that has been shown to have cognitive deficits</td>
</tr>
<tr>
<td></td>
<td>Stigma associated with ECT</td>
</tr>
</tbody>
</table>

c. Evidence-Based Pharmacologic Treatment Options (Appendix I):
   i. Combination AD + AP:
      1. Cochrane review (10 RCTs, n=548): combination AP + AD is more effective than AP alone (RR 1.92, 95% CI 1.32-2.80) but not more effective than AD alone (RR 1.44, 95% CI 0.86-2.41)
      2. At least 5 randomized controlled trials have shown greater response rate with combination therapy vs. monotherapy
      3. Combinations studied include:
         a. olanzapine + fluoxetine
         b. olanzapine + sertraline
         c. perphenazine + fluoxetine
         d. perphenazine + amitriptyline
         e. perphenazine + nortriptyline
   ii. Antidepressant monotherapy:
      1. At least 7 prospective studies including 5 randomized controlled trials:
         a. Positive results (typically in terms of response rate) found with: sertraline, paroxetine, fluvoxamine, imipramine, amitriptyline, nortriptyline, venlafaxine
         b. Poor response rate found with mirtazapine & with amitriptyline vs. amitriptyline/perphenazine
   iii. Antipsychotic monotherapy:
      1. Randomized controlled trials have shown poor response with AP monotherapy:
         a. Olanzapine monotherapy found to have significantly lower response rate (24-35%) than olanzapine/fluoxetine (64%) & olanzapine/sertraline (42%)22
         b. Perphenazine monotherapy found to have poor response rate (19%) vs. amitriptyline (41%) or combination (78%)19
   iv. Amoxapine:
      1. Only FDA approved agent for PMD
      2. Chemically related to midpotency 1st generation AP loxapine and has AD & AP properties
      3. Open trials and one randomized controlled trial have suggested efficacy in PMD35, 36
   v. Lithium augmentation:
      1. Positive results in 2 small studies:
         a. Nelson et al. (n=21): more effective in bipolar PMD (p=0.003)
         b. Price et al. (n=6): response rate of 50%
d. Duration of Treatment:
   i. Antipsychotic Therapy:
      1. Rothschild et al. \cite{39} AP therapy >4 months typically not required
         a. In patients with response to 5 weeks of perphenazine/fluoxetine treatment (n=30),
            perphenazine was tapered after 4 months with no relapse in 73% over 11 months
      2. DeBattista et al. \cite{36} 3 to 6 months after psychosis remits
      3. Risk of relapse:
         a. Open-label study in elderly patients (n=19).\cite{40} 25% (n=1) of responders to nortriptyline
            + perphenazine +/- lithium relapsed with perphenazine taper 16 weeks after
            response
         b. Retrospective study (n=52).\cite{41} 29% of 1st year relapses occurred during or shortly
            after AP taper (mean 2 months after mean exposure of 5 months) while maintained
            on stable dose of AD or lithium
   ii. Antidepressant Therapy:
      1. APA recommendations regarding continuation & maintenance phases of therapy for MDD
         should be followed\cite{6}
         a. Continuation phase: typically 4-9 months
         b. Maintenance phase:
            i. Duration depends on patient-specific factors
            ii. Indefinite treatment may be necessary for certain patient populations
            iii. Strongly consider for patients with additional risk factors for recurrence,
                including psychotic symptoms
      2. DeBattista & colleagues recommend chronic AD treatment unless poorly tolerated\cite{36}
      3. Risk of relapse:
         a. Open-label study in elderly patients (n=19).\cite{40} 53% relapse rate during continuation
            treatment with nortriptyline monotherapy over 2 years
         b. Maintenance treatment with fluvoxamine monotherapy (n=25) has been shown to
            prevent relapse over 6 months with 20% relapse over 2 years\cite{42}

   e. Potential Issues with Current Treatment Options:
      i. Relatively few treatments have demonstrated efficacy in treatment of PMD with low placebo response
         rates (typically 0-10% for 1 week of placebo run-in)\cite{36,43}
      ii. Wide range of response rates to current therapeutic options (~20 to 80%) with high
          relapse/recurrence rates for PMD compared to MDD\cite{5,36}
      iii. Potential delay in onset of action & lack of clearly defined optimal duration of therapy
      iv. Increased risk of ADRs with AP therapy in affective illness
      v. Increased potential for adverse effects & drug interactions with concomitant AP/AD therapy
         1. Few data from controlled studies address the longer term efficacy or side effects of long-term
            combination AP/AD therapy\cite{6}
         2. Increased incidence of tardive dyskinesia (43%), extrapyramidal symptoms & falls in geriatric
            patients with PMD treated with perphenazine + nortriptyline for 6 months\cite{25}
         3. Increased risk of other ADRs & drug interactions, for example:
            a. Increased potential for seizures with TCAs + certain APs (ex. clozapine)
            b. Increased risk of QTc prolongation (ex. citalopram + ziprasidone)
            c. Increased risk with certain combinations of additive anticholinergic effects, sedation,
               weight gain, orthostatic hypotension, etc.
            d. Potential interactions through cytochrome P450 enzymes
      vi. Increased cost of concomitant AP/AD therapy
         1. High cost of most 2nd generation antipsychotic medications + monitoring costs
I. MECHANISM OF ACTION IN PSYCHOTIC MAJOR DEPRESSION

a. Mifepristone is a potent antagonist at the low potency glucocorticoid receptor (GR, NR3C1) & progesterone receptor (PR, NR3C3) weak partial agonist \(^{11,44}\)

   i. Antiglucocorticoid properties lead to blocking of the feedback effect of cortisol on ACTH secretion which causes a rapid rise in cortisol
      1. Direct result: blocking the GR receptor leads to reduced transmission of this receptor, which directly leads to symptomatic & cognitive improvement
      2. Indirect result: cortisol floods the MR receptor, which leads to downregulation of this receptor & resets normal HPA axis rhythm

ii. Mifepristone has been shown to improve psychosis & depression in Cushing’s disease \(^{43}\)

iii. However, several studies evaluating mifepristone in PMD have assessed cortisol/ACTH levels & correlation with clinical response with inconclusive results \(^{43,16,45}\)

---

**Figure 2. Normal HPA Axis Function**

- MR: Mineralocorticoid receptor
- GR: Glucocorticoid receptor
- PVN: Paraventricular nucleus
- CRF: Corticotrophin releasing factor
- AVP: Arginine vasopressin
- ACTH: Adrenocorticotrophic hormone
- Glucocorticoids

MR= mineralocorticoid receptor; GR= glucocorticoid receptor; PVN= paraventricular nucleus; CRF= corticotrophin releasing factor; AVP= arginine vasopressin; ACTH= adrenocorticotrophic hormone
II. CLINICAL EVIDENCE

a. Summary of Small RCT & Open-Label Studies


<table>
<thead>
<tr>
<th>Design</th>
<th>Randomized, double-blind, single-center crossover study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Inpatients with DSM-IV diagnosis of PMD (n=5)</td>
</tr>
<tr>
<td>Interventions</td>
<td>AD/AP therapy prohibited during the study period</td>
</tr>
<tr>
<td></td>
<td>Randomized to mifepristone 600 mg daily for 4 days followed by 4 days of placebo or vice versa</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Improvement in Hamilton Rating Scale for Depression (HAM-D-21, Appendix II), Brief Psychiatric Rating Scale (BPRS, Appendix III) &amp; Clinical Global Impressions Scale (CGI)</td>
</tr>
<tr>
<td>Results</td>
<td>In all cases, HAMD-21 scores decreased with mifepristone treatment with mean decrease of 8.0 (25.5%) for mifepristone vs. 1.7 (5.8%) for placebo (p&lt;0.07)</td>
</tr>
<tr>
<td></td>
<td>BPRS scores decreased in 4 of 5 cases with mean decrease in mifepristone group of 10.2 points (34%) vs. 0.3 points (1.2%) for placebo (p-value not reported)</td>
</tr>
<tr>
<td>Take Home Points</td>
<td>A 4-day course of mifepristone led to a decrease in HAMD-21 and BPRS scores in 5 inpatients with PMD, although not statistically significant</td>
</tr>
<tr>
<td></td>
<td>Patients were still symptomatic &amp; all patients required AD therapy following the study</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Design</th>
<th>Phase II, open-label randomized trial at six academic medical centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Inpatients with DSM-IV diagnosis of PMD &amp; HAMD-21 score ≥ 18 (n=30)</td>
</tr>
<tr>
<td></td>
<td>Treatment naive or on stable doses of AD and/or AP for ≥ 1 week</td>
</tr>
<tr>
<td>Interventions</td>
<td>Randomized to mifepristone 50 mg, 600 mg, or 1200 mg daily for 7 days</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Response criteria: 30% reduction on BPRS, 50% reduction on BPRS Positive Symptom Subscale (BPRS-PSS), &amp; 50% reduction on HAMD-21 from day 0 to day 7</td>
</tr>
<tr>
<td>Results</td>
<td>Baseline medications: AD + AP (n=19); AP (n=3); AD (n=1); none (n=7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>50 mg</th>
<th>600 mg</th>
<th>1200 mg</th>
<th>600 mg + 1200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D Response</td>
<td>2/11 (18.2%)</td>
<td>5/10 (50%)</td>
<td>3/9 (33%)</td>
<td>8/19 (42.1%)</td>
</tr>
<tr>
<td>BPRS Response</td>
<td>4/11 (36.4%)</td>
<td>7/10 (70%)</td>
<td>6/9 (66.7%)</td>
<td>13/19 (68.4%)</td>
</tr>
<tr>
<td>BPRS-PSS Response</td>
<td>3/11 (27.3%)</td>
<td>6/10 (60%)</td>
<td>6/9 (66.7%)</td>
<td>12/19 (63.2%)</td>
</tr>
<tr>
<td>Take Home Points</td>
<td>A 7-day course of mifepristone in severely depressed inpatients showed potential benefit for depressive symptoms (&gt;40% of patients on &gt; 600 mg with HAMD-21 response) as well as psychotic symptoms (&gt;60% of patients on &gt; 600 mg with BPRS-PSS response)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Design</th>
<th>8-week, open-label trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Inpatients with DSM-IV diagnosis of PMD &amp; HAMD-21 ≥ 23 (n=20)</td>
</tr>
<tr>
<td>Interventions</td>
<td>AP/AD therapy prohibited for ≤ 1 week prior to baseline ratings &amp; throughout the study</td>
</tr>
<tr>
<td></td>
<td>Mifepristone 200 mg PO TID for 6 days</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Improvement in HAMD-21, CGI &amp; BPRS scores</td>
</tr>
<tr>
<td></td>
<td>Response, defined as reduction in HAMD-21 score to ≤ 50% of baseline</td>
</tr>
<tr>
<td></td>
<td>Remission, defined as HAMD-21 score &lt; 7</td>
</tr>
<tr>
<td>Results</td>
<td>Significant improvement in HAMD-21 &amp; CGI scores after weeks 1, 4, &amp; 8 (p&lt;0.001) &amp; in BPRS scores after weeks 4 &amp; 8 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Response: 2 subjects at week 1; all 18 remaining subjects at week 4</td>
</tr>
<tr>
<td></td>
<td>Remission: 1 subject at week 1; 11 subjects at week 4; 3 subjects at week 8 (but 1 subject dropped to response)</td>
</tr>
<tr>
<td>Take Home Points</td>
<td>Mifepristone 200 mg three times daily for 6 days led to a statistically significant decrease in HAMD-21, BPRS, &amp; CGI scores in severely depressed inpatients with psychotic features</td>
</tr>
<tr>
<td></td>
<td>At week 4, 18 of 20 patients met criteria for response &amp; 11 of 18 patients met criteria for remission</td>
</tr>
</tbody>
</table>
b. Literature Review:


### Design
- Randomized, double-blind, placebo-controlled trial

### Objective(s)
- To determine the efficacy of mifepristone on psychotic symptoms in PMD

### Population
- n=30
- Inpatients & outpatients with diagnosis of PMD

### Inclusion Criteria
- PMD diagnosis based on clinical interview data, Structured Clinical Interview for the DSM-IV (SCID) data & BPRS ratings
- Score of > 21 on HAMD-21 & > 5 on BPRS Positive Symptom Subscale (BPRS-PSS)

### Exclusion Criteria
- Less than 18 years of age
- Pregnant/lactating females
- Patients taking medications that may directly interfere with mifepristone metabolism such as systemic steroids & antifungual medications
- Patients with: active suicidality, Obsessive-Compulsive Disorder, major medical illnesses, history of seizures, major head traumas, or abnormal clinical laboratory tests

### Interventions
- Randomized to mifepristone 600 mg daily or placebo for 8 days
- Allowed to remain on current treatment regimen if stable for > 2 weeks prior to screening
- HAMD-21 & BPRS rated by blinded, trained clinical administrator on day 0 & day 8
- Safety: clinical laboratory tests performed in eligibility screening & after treatment completed; monitored daily for ADRs

### Endpoints
- Primary: 50% reduction on BPRS-PSS
- Secondary: 30% reduction on BPRS total score; 50% reduction on HAMD-21

### Statistical Analysis
- One-way ANOVA or Chi-square analyses used for baseline characteristics
- Chi-square analysis used to determine difference in dichotomous clinical response & repeated-measures ANOVA used to analyze changes in scores on psychiatric measures
- Gender differences determined using one-way ANOVA; association with age determined using Pearson correlation; effect sizes calculated using Cohen’s d
- Two-tailed alpha = 0.05

### Results

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Mifepristone (n=15)</th>
<th>Placebo (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years (SD))</td>
<td>36.4 (13.2)</td>
<td>38.8 (12.9)</td>
</tr>
<tr>
<td>Education (years (SD))</td>
<td>14.8 (2.8)</td>
<td>15.4 (3.4)</td>
</tr>
<tr>
<td>Male (n)</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Female (n)</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Caucasian (n)</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>African-American (n)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic (n)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Asian/Pacific Islander (n)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

- No statistically significant difference in current medications between groups
  - Included: AD alone (10%), AP alone (13.3%), AD + anxiolytic (3.3%), AD + AP (46.7%), AD + AP + mood stabilizer (16.7%), & anxiolytic alone or no medication (10%)

### Psychiatric Rating Scale Scores at Baseline & Day 8

<table>
<thead>
<tr>
<th></th>
<th>Mifepristone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n=15)</td>
<td>Day 8 (n=15)</td>
</tr>
<tr>
<td>BPRS-PSS (mean (SD))</td>
<td>12.6 (3.94)</td>
<td>8.9 (3.42)</td>
</tr>
<tr>
<td>BPRS total (mean (SD))</td>
<td>46.9 (5.69)</td>
<td>38.5 (9.61)</td>
</tr>
<tr>
<td>HAMD-21 (mean (SD))</td>
<td>29.3 (5.00)</td>
<td>21.3 (7.14)</td>
</tr>
</tbody>
</table>

- Using repeated measures ANOVA, significant main effect of time found on BPRS (total score & BPRS-PSS, p<0.01) & HAMD-21 (p<0.001) showing significant clinical improvement in the mifepristone group & placebo group at day 8
  - No significant main effect found for medication or medication-by-time interaction
### Results (cont.)
- **Safety:**
  - 1 patient dropped out due to worsening of pre-existing constipation
  - ADRs (n):
    - Mifepristone: rash (4), fatigue (2), decreased appetite (1), irritability/agitation (2), constipation (2), dysmenorrhea (1)
    - Placebo: nausea (1), increased appetite (1), fatigue (1)

### Author's Conclusions
"These results suggest that short-term use of mifepristone may be effective in the treatment of PMD. Additional blinded studies are warranted."

### Strengths
- Randomized, controlled study design
- Inclusion based on severity of psychosis (BPRS-PSS score) in addition to HAMD-21 score
- Included females of childbearing potential unless pregnant/lactating
- Assessed response using multiple psychiatric rating scales with focus on psychotic symptoms through assessment of BPRS-PSS as primary endpoint
- Statistical significance determined for response rates

### Limitations
- Small sample size
- Concomitant AP/AD therapy & significant variability in baseline medications
  - Difficult to assess whether mifepristone led to improvement
- Endpoints only assessed after 8 days of therapy
  - No longer term endpoints
- Placebo response higher than usual reported placebo response for PMD

### Take Home Points
- Significantly more patients in the mifepristone group met response criteria on the BPRS-PSS vs. placebo, showing potential benefit for psychotic symptoms in severely depressed patients
- Mifepristone did not lead to a statistically significant change in depressive symptoms as assessed by HAMD-21 response

---


### Design
- Double-blind, multicenter (29 sites in the U.S.), randomized, placebo controlled, parallel-group trial

### Objective(s)
- To compare the efficacy of mifepristone with placebo on psychotic symptoms in patients with PMD on no concomitant AP/AD therapy

### Population
- n=221
- Patients with DSM-IV diagnosis of PMD
- Patient were hospitalized for the 1st 3 days, then could be treated as outpatient or inpatient

### Inclusion Criteria
- Age 19 to 75 years
- Patients meeting DSM-IV criteria for PMD by clinical interview & SCID; confirmed via review of hospital admission notes
- ≥38 on BPRS & ≥20 on HAMD-24
- Females with negative serum pregnancy test & agreement to use of 2 acceptable methods of contraception during study period

### Exclusion Criteria
- Unstable medical condition
- Use of systemic or inhaled corticosteroids
- ECT in the 3 months prior to randomization
- APs/AD use within 7 days prior to randomization or during days of mifepristone administration
- History of illicit drug use in the previous month or alcohol/drug dependence in the previous 6 months

### Interventions
- Randomized 1:1 to mifepristone 600 mg daily (n=105) or placebo (n=116) for 7 days followed by 21 days of usual treatment
- BPRS & HAMD-24 performed on days 0, 3, 7, 14, & 28
- Subset of patients had efficacy measures at day 56 to further assess durability of response
- Efficacy measures assessed for subset of patients with BPRS-PSS ≥ 12
- From day 8 onward, any medication could be prescribed

### Endpoints
- Primary endpoint: a priori defined "responder analysis"
  - Comparison of percentage of patients with Rapid Response (≥30% reduction in BPRS on days 7 & 28), Response (≥30% reduction in BPRS at day 28 but not day 7) and No Response
- Secondary endpoints: 50% reduction in BPRS-PSS & 50% reduction in HAMD-24 at day 7 & sustained through day 28
- Safety: spontaneous report of ADRs, physical examination & laboratory assessments
Statistical Analysis

- Intention-to-treat design with mixed model for repeated measurements (MMRM) model used to impute missing data (n=51)
- Cochran-Mantel-Haenszel (CMH) test used to analyze the “responder analysis” across treatments, adjusting for site
- CMH test performed separately for 2 subsets of patients:
  - More severe psychotic symptoms (defined as BPRS-PSS > 12 at baseline) (n=159)
  - Patients completing follow-up efficacy assessment at day 56 (n=42)
- Two-tailed alpha = 0.05

Results

- No significant differences in baseline characteristics
- No significant difference after day 7 in rate of AD use (58% mifepristone vs. 62% placebo), AP use (36% vs. 42%) combination (29% vs. 37%) or ECT use (2% vs. 3%)

### Patient Characteristics (ITT sample, n=221)

<table>
<thead>
<tr>
<th></th>
<th>Mifepristone (n=105)</th>
<th>Placebo (n=116)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean (SD))</td>
<td>40.9 (10.8)</td>
<td>41.6 (11.0)</td>
<td>0.62a</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>56 (53.3)</td>
<td>56 (48.3)</td>
<td>0.45b   for gender</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>49 (46.7)</td>
<td>60 (51.7)</td>
<td></td>
</tr>
<tr>
<td>White (n, %)</td>
<td>57 (54.3)</td>
<td>59 (50.9)</td>
<td>0.74c   for ethnicity</td>
</tr>
<tr>
<td>Black (n, %)</td>
<td>38 (36.2)</td>
<td>42 (36.2)</td>
<td></td>
</tr>
<tr>
<td>Asian (n, %)</td>
<td>1 (1.0)</td>
<td>4 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino (n, %)</td>
<td>9 (8.6)</td>
<td>10 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Baseline Measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS total (SD)</td>
<td>55.8 (11.6)</td>
<td>55.7 (9.2)</td>
<td>0.56a</td>
</tr>
<tr>
<td>BPRS-PSS (SD)</td>
<td>13.7 (3.6)</td>
<td>13.4 (3.2)</td>
<td>0.95a</td>
</tr>
<tr>
<td>HAMD (SD)</td>
<td>37.3 (8.4)</td>
<td>37.3 (7.5)</td>
<td>0.96a</td>
</tr>
</tbody>
</table>

a= significance level from a one-way ANOVA with treatment as a factor; b= Fisher’s exact test; c= Pearson chi-square test

### Primary & Secondary Endpoints: Response Status by Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>ITT Observed Cases</th>
<th>Placebo Observed Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mifepristone (n=105)</td>
<td>Placebo (n=116)</td>
</tr>
<tr>
<td>BPRS Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid &amp; Sustained</td>
<td>51 (48.6%)</td>
<td>49 (42.2%)</td>
</tr>
<tr>
<td>Response</td>
<td>31 (29.1%)</td>
<td>23 (19.8%)</td>
</tr>
<tr>
<td>Non-response</td>
<td>23 (21.9%)</td>
<td>44 (37.9%)</td>
</tr>
<tr>
<td>p-value = 0.041</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS-PSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid &amp; Sustained</td>
<td>50 (47.6%)</td>
<td>40 (34.5%)</td>
</tr>
<tr>
<td>Response</td>
<td>23 (21.9%)</td>
<td>17 (14.7%)</td>
</tr>
<tr>
<td>Non-response</td>
<td>32 (30.5%)</td>
<td>59 (50.9%)</td>
</tr>
<tr>
<td>p-value = 0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAMD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid &amp; Sustained</td>
<td>50 (47.6%)</td>
<td>56 (48.3%)</td>
</tr>
<tr>
<td>Response</td>
<td>21 (20.0%)</td>
<td>15 (12.9%)</td>
</tr>
<tr>
<td>Non-response</td>
<td>34 (32.4%)</td>
<td>45 (38.8%)</td>
</tr>
<tr>
<td>p-value = 0.668</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a= from CMH test adjusted by pooled site

- Subset with BPRS-PSS ≥ 12 (n=159): significantly more mifepristone patients had a rapid reduction in psychotic symptoms, measured by the BPRS-PSS by day 7 and sustained at day 28 (p=0.001 ITT; p=0.003 observed cases)

### Patients with Baseline PSS Scores > 12 (n=159): Response Status by Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>ITT Observed Cases</th>
<th>Placebo Observed Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mifepristone (n=74)</td>
<td>Placebo (n=85)</td>
</tr>
<tr>
<td>BPRS-PSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid &amp; Sustained</td>
<td>43 (58.1%)</td>
<td>28 (32.9%)</td>
</tr>
<tr>
<td>Response</td>
<td>11 (14.9%)</td>
<td>11 (12.9%)</td>
</tr>
<tr>
<td>Non-response</td>
<td>20 (27.0%)</td>
<td>46 (54.1%)</td>
</tr>
<tr>
<td>p-value = 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a= from CMH test adjusted by pool site
Results (cont.)

- Subset observed at day 56 (n=42):
  - 53% of mifepristone group vs 22% of placebo group responded (according to BPRS) by day 7 & sustained the response at day 56 (p=0.038)
  - Mean change from baseline BPRS-PSS scores at day 7 (p=0.028) & day 56 (p=0.007) were significantly different between groups; trend favoring mifepristone on improvement in HAMD-24 change from baseline at day 56 (p=0.056)

- Safety:
  - No significant difference between groups in adverse effects
  - 1 patient from each group dropped out due to adverse effects

### Adverse Events (> 5% for any group)

<table>
<thead>
<tr>
<th>ADE</th>
<th>Mifepristone n (%)</th>
<th>Placebo n (%)</th>
<th>Total n (%)</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Studied</td>
<td>105 (67.6)</td>
<td>116 (73.3)</td>
<td>221 (70.6)</td>
<td></td>
</tr>
<tr>
<td>Total Patients Studied</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Patients with ADEs</td>
<td>71 (67.6)</td>
<td>85 (73.3)</td>
<td>156 (70.6)</td>
<td></td>
</tr>
</tbody>
</table>

- Headache: 17 (16.2) vs 21 (18.1) vs 38 (17.2) (p=0.73)
- Nausea: 12 (11.4) vs 7 (6.0) vs 19 (8.6) (p=0.23)
- Vomiting: 10 (9.5) vs 5 (4.3) vs 15 (6.8) (p=0.18)
- Constipation: 5 (4.8) vs 12 (10.3) vs 17 (7.7) (p=0.14)
- Dizziness: 6 (5.7) vs 10 (8.6) vs 16 (7.2) (p=0.45)
- Insomnia: 5 (4.8) vs 6 (5.2) vs 11 (5.0) (p=1.00)
- Sedation: 7 (6.7) vs 8 (6.9) vs 15 (6.8) (p=1.00)
- Abdominal Pain NOS: 6 (5.7) vs 4 (3.4) vs 10 (4.5) (p=0.52)
- Abdominal Pain Upper: 1 (1.0) vs 2 (1.7) vs 8 (3.6) (p=0.16)
- Rash: 6 (5.7) vs 6 (5.2) vs 7 (3.2) (p=0.12)
- Toothache: 6 (5.7) vs 1 (0.9) vs 7 (3.2) (p=0.06)

a= the denominator for the percentages is the total number of patients in each treatment; b= Fisher’s exact

### Author’s Conclusions

“A seven day course of mifepristone followed by usual treatment appears to be effective and well tolerated in the treatment of psychosis in PMD. This study suggests that mifepristone might represent an alternative to traditional treatments of psychosis in psychotic depression.”

### Strengths

- Randomized, controlled study design
- Large sample size
- Concurrent AP/AD therapy prohibited prior to or during mifepristone therapy
- Inclusion based on BPRS score in addition to HAMD-24 score
- Females of childbearing potential included if negative serum pregnancy test
- Assessed response rate at several time points after treatment period
  - Determination of more prolonged response relative to previous studies
- Statistical significance determined for response rates
- Assessed response using multiple psychiatric rating scales with focus on psychotic symptoms through assessment of BPRS (although not BPRS-PSS) as primary endpoint

### Limitations

- AP/AD therapy allowed after day 7 although efficacy was determined up to day 56
  - Inconsistency in interpreting results on psychotic/depressive symptoms
- Risk of misestimation due to imputation of missing data
- Very high placebo response rates

### Take Home Points

- Patients in the mifepristone group were significantly more likely to achieve rapid and sustained response on BPRS total score, as well as secondary measure of BPRS-PSS response
  - Potential benefit for psychotic symptoms in severely depressed patients with moderate to severe psychotic symptoms
- No statistically significant change in depressive symptoms as determined by secondary endpoint of change in HAMD-24 score
- Mifepristone was well tolerated

---


**Design**

- 8-week randomized, multicenter (29 sites in the U.S. & Eastern Europe), double-blind clinical trial

**Objective(s)**

- To determine the efficacy of mifepristone for the treatment of PMD in a population with moderate to severe psychotic symptoms
- To explore the relationship between clinical response & plasma concentrations of mifepristone
Population
- n=258
- DSM-IV & SCID diagnosis of PMD

Inclusion Criteria
- Patients meeting DSM-IV & SCID criteria for PMD
- Baseline BPRS score > 38, BPRS-PSS score > 12 & HAMD-24 score > 20

Exclusion Criteria
- Not noted

Interventions
- Randomized 1:1 to mifepristone 600 mg daily or placebo for 7 days
- Antidepressant therapy required for 7 weeks following mifepristone therapy; antipsychotic therapy prohibited throughout the study
- BPRS-PSS assessed by certified trained raters at baseline & on day 7, 14, 28 & 56
- Trough plasma concentrations were determined through blood samples obtained before dosing on day 7

Endpoints
- Primary outcome: rapid and sustained response, defined as > 50% decrease in BPRS-PSS score at the end of treatment (day 7) and 49 days later (day 56)
- Secondary outcomes: rapid and sustained response for the original sites (without 9 sites added late in the study) and for the added sites; response rates for patients with mifepristone concentration > 1800 ng/mL

Statistical Analysis
- Sample size was determined a priori based on effect sizes observed in DeBattista study
- CMH used to compare proportions of responders to mifepristone vs. placebo adjusting for site
- The Breslow–Day test was used to test for heterogeneity in the odds ratios
- ITT principle with missing data replaced using “worst case” and MMRM methods
- Exploratory analyses compared response of patients with mifepristone plasma concentrations of ≥1800 ng/mL to placebo
  - Plasma level optimally correlating with clinical response determined via post-hoc analysis

Results

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Mifepristone</th>
<th>Placebo</th>
<th>Original Sites</th>
<th>Added Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat, N</td>
<td>131</td>
<td>126</td>
<td>215</td>
<td>42</td>
</tr>
<tr>
<td>Observed cases, N</td>
<td>113</td>
<td>97</td>
<td>178</td>
<td>32</td>
</tr>
<tr>
<td>Age (mean (SD))</td>
<td>43.6 (13)</td>
<td>43.5 (12)</td>
<td>43 (13)</td>
<td>46 (11)</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>55</td>
<td>60</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Race/ethnicity (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>African American</td>
<td>50</td>
<td>44</td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Caucasian</td>
<td>64</td>
<td>62</td>
<td>96</td>
<td>35</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>12</td>
<td>13</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Baseline Measures (mean)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS total (SD)</td>
<td>53.6 (7)</td>
<td>54.2 (7)</td>
<td>35.7 (7)</td>
<td>36.6 (8)</td>
</tr>
<tr>
<td>BPRS-PSS (SD)</td>
<td>15.0 (2)</td>
<td>14.8 (2)</td>
<td>14.9 (2)</td>
<td>14.6 (2)</td>
</tr>
<tr>
<td>HAMD-24 (SD)</td>
<td>37.1 (7)</td>
<td>37.9 (7)</td>
<td>37.5 (7)</td>
<td>37.2 (8)</td>
</tr>
</tbody>
</table>

- Statistical difference between groups not assessed for baseline characteristics
- There was an acceleration in recruitment towards the end of the study which correlated with late addition of 9 sites

### Response Rates on Primary Endpoint (BPRS-PSS)^

<table>
<thead>
<tr>
<th>n</th>
<th>Missing Data Replacement</th>
<th>Response Mifepristone</th>
<th>Response Placebo</th>
<th>Not Adjusted for Site</th>
<th>Adjusted for Site</th>
<th>Site by Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT 257</td>
<td>MMRM</td>
<td>31%</td>
<td>29%</td>
<td>0.730</td>
<td>0.753</td>
<td>0.020</td>
</tr>
<tr>
<td>ITT 257</td>
<td>Worst Case</td>
<td>26%</td>
<td>17%</td>
<td>0.096</td>
<td>0.096</td>
<td>0.140</td>
</tr>
<tr>
<td>Observed Cases  210</td>
<td>None</td>
<td>30%</td>
<td>23%</td>
<td>0.226</td>
<td>0.370</td>
<td>0.039</td>
</tr>
</tbody>
</table>

a= ≥50% reduction in BPRS-PSS scores at day 7 & day 56; b= significance comparing response to mifepristone & placebo; both unadjusted & adjusted for the main effects of site; c= significance levels for the site-by-treatment interactive effect
### Results (cont.)

#### Response Rates for Patients Enrolled at Original Sites & Added Sites

<table>
<thead>
<tr>
<th>Analysis Population</th>
<th>n</th>
<th>Imputation</th>
<th>Response Mifepristone</th>
<th>Response Placebo</th>
<th>p-value (CMH)</th>
<th>p-value (CMH Adjusted for Site)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Sites-ITT</td>
<td>215</td>
<td>Worst Case</td>
<td>26%</td>
<td>13%</td>
<td>0.023</td>
<td>0.014</td>
</tr>
<tr>
<td>Original Sites-Observed</td>
<td>178</td>
<td>None</td>
<td>30%</td>
<td>17%</td>
<td>0.048</td>
<td>0.059</td>
</tr>
<tr>
<td>Added Sites-ITT</td>
<td>42</td>
<td>Worst Case</td>
<td>27%</td>
<td>40%</td>
<td>0.384</td>
<td>0.483</td>
</tr>
<tr>
<td>Added Sites-Observed</td>
<td>32</td>
<td>None</td>
<td>33%</td>
<td>57%</td>
<td>0.184</td>
<td>0.242</td>
</tr>
</tbody>
</table>

*a* = >50% reduction in BPRS-PSS scores at day 7 & 56

#### Response Rates for Patients with Mifepristone Concentration > 1800 ng/mL

<table>
<thead>
<tr>
<th>Observed Cases</th>
<th>n</th>
<th>Response Mifepristone</th>
<th>Response Placebo</th>
<th>p-value (CMH)</th>
<th>p-value (CMH adjusted for site)</th>
<th>p-value (Breslow-Day: site x treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Sites</td>
<td>207</td>
<td>41%</td>
<td>23%</td>
<td>0.031</td>
<td>0.094</td>
<td>0.089</td>
</tr>
<tr>
<td>Original Sites</td>
<td>176</td>
<td>46%</td>
<td>17%</td>
<td>0.002</td>
<td>0.001</td>
<td>0.84</td>
</tr>
</tbody>
</table>

*a* = observed cases: patients with observed efficacy & plasma concentration data; *b* = 3 patients of the n=210 at all sites with observed efficacy data were missing drug plasma concentrations vs. 2 patients of the n=178 observed cases at original sites were missing drug plasma concentrations

- Plasma trough concentrations ranged from 0 to 4559 (mean=1671, SD=780) with approximately one-third of patients achieving concentrations higher than the pre-specified level of 1800 ng/mL
  - Plasma concentration & efficacy association was statistically significant in the ITT sample (OR=2.4, *p*=.030)
  - Post hoc analysis indicated that the optimum plasma level for distinguishing responders from non-responders was 1661 ng/ml
    - In patients with concentrations ≥1661, response rate was 42% (mifepristone) vs. 17% (placebo) (*p*=0.018)

#### Author’s Conclusions

“This study reminds trialists to formally evaluate the interaction of site-by-treatment. In addition, the association between increased mifepristone plasma concentration levels and greater clinical response, detected despite the site-by-treatment interaction, suggests that higher plasma levels may be needed for maximizing the probability of a positive response.”

#### Strengths

- Randomized, controlled study design
- Large sample size
- Assessed response rate at several time points after treatment period (determination of prolonged response)
- Statistical significance determined for response rates
- Inclusion based on BPRS score and BPRS-PSS score in addition to HAMD-24 score
- AP prohibited throughout the study period & consistency in AD therapy (AD required)
- Focused on effect of mifepristone on psychotic symptoms through assessment of BPRS-PSS as primary endpoint

#### Limitations

- Safety not assessed
- Exclusion criteria not noted
- Multicenter design may have impacted validity of results as determined by significant site-by-treatment interaction
- No explanation regarding determination of predefined plasma concentration of 1800 ng/mL & doses correlating with plasma concentrations not reported
- No power calculation
- Lack of reasoning for use of HAMD-24 vs. HAMD-21
- Risk of misestimation due to imputation of missing data

#### Take Home Points

- No statistically significant change in psychotic symptoms as assessed by BPRS-PSS response between mifepristone (26-31%) and placebo (17-29%) in inpatients with severe depression and moderate to severe psychotic symptoms
  - Significant site-by-treatment interaction may preclude interpretation of results
- Questionable association between mifepristone plasma concentrations & clinical response
c. **Safety Issues:**
   i. Reported ADRs:
      1. Typically benign (rash, uterine cramping, fatigue, anorexia, nausea)
      2. Contraindications: a. Chronic adrenal failure  
         b. Porphyrias  
         c. Hemorrhagic disorders or concurrent anticoagulant therapy  
         d. Intrauterine device (IUD) in place
   ii. Requirement for pregnancy testing in females of child-bearing age
      1. Black box warnings for rare but potentially life-threatening bleeding or infections when mifepristone is used as an abortifascient (medication guide required)
   iii. Drug Interactions:  
      1. Contraindicated with concomitant corticosteroids  
      2. Potential interactions through CYP 3A4
   iv. Little known about repeated exposure in patients who relapse

d. **Current Status:**
   i. Phase III trials sponsored by Corcept Therapeutics under brand name Corlux™ or Korlym™
   ii. Five completed Phase III trials: results not available
   iii. Currently recruiting:
      1. “A Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Corlux (Mifepristone) vs. Placebo in the Treatment of Psychotic Symptoms in Patients With Major Depressive Disorder With Psychotic Features”  
         a. Mifepristone 1200 mg daily vs. placebo for 7 days followed by AD therapy  
         b. Estimated completion date: April 2013

---

**Summary: Does Mifepristone Have a Place in Therapy for PMD?**

I. **TARGETED PLACE IN THERAPY**
   i. Alternative to AP therapy in combination with AD therapy
   ii. More rapid response vs. current treatment options (?)
   iii. Potential benefit for patients who:
      1. Are unable to tolerate AP therapy
      2. Desire a shorter course of therapy for treatment of psychotic symptoms

II. **ISSUES WITH CLINICAL EVIDENCE**

a. **Response Rates:**
   i. Mifepristone response rates:
      1. HAMD response ranging from around 27% to 100% (not statistically significant)  
      2. BPRS response ranging from around 50% to 78%  
         a. Statistically significant response (78%) in DeBattista study only  
      3. BPRS-PSS response ranging from around 30% to 70%  
         a. Statistically significant in Flores (47%) & DeBattista (70%) studies
   ii. Comparable response rates to current treatment options for PMD
      1. 42% to 78% response rates with combination AP/AD  
      2. Variation in rating scale(s) used to assess response  
         a. Majority used HAMD +/- rating scales for psychotic symptoms
   iii. Lack of validation for BPRS scale in PMD & questionable definition of response
      1. One recommendation that studies in patients with schizophrenia and positive symptoms should use a 50% reduction cut-off to define response  
      2. BPRS lacks clearly defined operational criteria for different levels of severity & overlap can occur
   iv. Questionable durability of response & risk of relapse
b. **Variability in:**
   - i. Dosing & duration of mifepristone
   - ii. Duration of study period
   - iii. Psychiatric rating scale used to assess primary endpoint
   - iv. Determination of response & statistical analysis of response as primary endpoint
   - v. Concurrent AP/AD therapy prior to & during the study period
   - vi. Inclusion/exclusion of females of childbearing potential
   - vii. Inclusion based on severity of psychotic symptoms in addition to severity of depression
   - viii. Results regarding efficacy for depressive vs. psychotic symptoms

**Conclusions**

I. PMD is a severe mood disorder associated with significant morbidity & mortality and evidence-based treatment options are lacking

II. Mifepristone is a potential treatment option for PMD

III. Lack of sufficient evidence based on results of currently available evidence to recommend a change in clinical practice

IV. Watch for results of ongoing & completed Phase III trials
References


## APPENDIX I. Summary of Literature on Pharmacotherapeutic Options for Treatment of PMD

<table>
<thead>
<tr>
<th>Authors</th>
<th>Intervention</th>
<th>Population</th>
<th>Study Design</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combination AD + AP</strong></td>
<td>**Rothschild et al.**26</td>
<td>Fluoxetine + perphenazine</td>
<td>Unipolar &amp; bipolar (n=30)</td>
<td>Prospective study (5 weeks) 73% response rate</td>
</tr>
<tr>
<td>**Spiker et al.**19</td>
<td>Amitriptyline vs. perphenazine vs. combination</td>
<td>Inpatients with PMD (n=51)</td>
<td>RCT (35 days)</td>
<td>Response rate: 78% combination vs. 41% amitriptyline vs. 19% perphenazine</td>
</tr>
<tr>
<td>**Rothschild et al.**50</td>
<td>Olanzapine vs. other APs (80% of patients taking AD)</td>
<td>Inpatients; bipolar &amp; unipolar (n=30)</td>
<td>Retrospective</td>
<td>Improvement in 67% olanzapine vs. 27% other APs (p=0.037)</td>
</tr>
<tr>
<td>**Meyers et al.**22</td>
<td>Olanzapine + sertraline or placebo</td>
<td>Inpatients with PMD (n=259)</td>
<td>RCT (12 weeks)</td>
<td>Remission rate: 42% combination vs. 24% monotherapy (p=0.002)</td>
</tr>
<tr>
<td>**Mulsant et al.**23</td>
<td>Nortriptyline + perphenazine or placebo</td>
<td>Inpatients with PMD (n=54)</td>
<td>RCT (4 weeks)</td>
<td>Response rate: 50% combination vs 44% monotherapy</td>
</tr>
<tr>
<td>**Rothschild et al.**24</td>
<td>Olanzapine vs. olanzapine + fluoxetine vs. placebo</td>
<td>Inpatient &gt; 1 week; unipolar PMD (n=249)</td>
<td>RCT (8 weeks)</td>
<td>Olanzapine/fluoxetine higher response rate (64%) vs. olanzapine (35%, p=0.027) or placebo (28%, p=0.004)</td>
</tr>
<tr>
<td>**Meyers et al.**25</td>
<td>Continuation therapy: nortriptyline + perphenazine or placebo after remission with ECT</td>
<td>Geriatric patients with PMD (n=29)</td>
<td>RCT</td>
<td>Greater relapse rate &amp; adverse effects with combination therapy</td>
</tr>
<tr>
<td><strong>AD Monotherapy</strong></td>
<td>**Zanardi et al.**27</td>
<td>Sertraline vs. paroxetine</td>
<td>Inpatients; bipolar &amp; unipolar (n=46)</td>
<td>RCT (6 weeks) 75% sertraline vs. 46% paroxetine (p=0.16)</td>
</tr>
<tr>
<td>**Avery et al.**31</td>
<td>Imipramine then ECT in nonresponders</td>
<td>Inpatients with depression (n=437)</td>
<td>Prospective study (25 days)</td>
<td>In delusional depression (n=181): 40% improved with imipramine; 83% (n=109) after ECT</td>
</tr>
<tr>
<td>**Chan et al.**51</td>
<td>Various TCAs</td>
<td>Inpatients with depression (n=75)</td>
<td>Retrospective chart review</td>
<td>In psychotic depression (n=16): 25% response rate</td>
</tr>
<tr>
<td>**Zanardi et al.**29</td>
<td>Venlafaxine vs. fluvoxamine</td>
<td>Inpatients; bipolar &amp; unipolar (n=28)</td>
<td>RCT (6 weeks)</td>
<td>Response rates: 79% fluvoxamine vs. 58% venlafaxine (p=0.4)</td>
</tr>
<tr>
<td>**Van den Broek et al.**32</td>
<td>Imipramine vs. fluvoxamine (predefined levels)</td>
<td>Inpatients with PMD (n=141)</td>
<td>RCT (4 weeks)</td>
<td>Greater improvement on CGI with imipramine (p=0.048)</td>
</tr>
<tr>
<td>**Bruijn et al.**33</td>
<td>Imipramine vs. mirtazapine</td>
<td>Inpatients; bipolar &amp; unipolar (n=107)</td>
<td>RCT (4 weeks)</td>
<td>Response rate: 22% mirtazapine vs. 50% imipramine (p=0.007)</td>
</tr>
<tr>
<td>**Spiker et al.**34</td>
<td>Amitriptyline vs. placebo</td>
<td>Inpatients with PMD (n=27)</td>
<td>RCT (4 weeks)</td>
<td>Amitriptyline superior to placebo (p&lt;0.05)</td>
</tr>
<tr>
<td>**Gatti et al.**30</td>
<td>Fluvoxamine vs. placebo</td>
<td>Inpatients with PMD (n=57)</td>
<td>Prospective (6 weeks)</td>
<td>Recovery rate 84%</td>
</tr>
<tr>
<td>**Simpson et al.**28</td>
<td>Sertraline monotherapy</td>
<td>Inpatients with PMD (n=25)</td>
<td>Open-label (8 weeks)</td>
<td>Greater remission (p=0.001) &amp; response (p=0.011) for MDD vs. PMD</td>
</tr>
<tr>
<td><strong>AP Monotherapy</strong></td>
<td>**Rothschild et al.**24</td>
<td>Olanzapine vs. olanzapine + fluoxetine vs. placebo</td>
<td>Inpatient &gt; 1 week; unipolar PMD (n=249)</td>
<td>RCT (8 weeks) Olanzapine/fluoxetine higher response rate (64%) vs. olanzapine (35%, p=0.027) or placebo (28%, p=0.004)</td>
</tr>
<tr>
<td>**Spiker et al.**19</td>
<td>Amitriptyline vs. perphenazine vs. combination</td>
<td>Inpatients with PMD (n=51)</td>
<td>RCT (35 days)</td>
<td>Response rate: 78% combination vs. 41% amitriptyline vs. 19% perphenazine</td>
</tr>
<tr>
<td>**Meyers et al.**22</td>
<td>Olanzapine + sertraline or placebo</td>
<td>Inpatients with PMD (n=259)</td>
<td>RCT (12 weeks)</td>
<td>Remission rate: 42% combination vs. 24% monotherapy (p=0.002)</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>Amoxapine vs amitriptyline + perphenazine</td>
<td>Inpatients with PMD (n=46)</td>
<td>RCT (4 weeks)</td>
<td>Similar improvements in depression &amp; psychosis; amoxapine better tolerated</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------</td>
<td>-----------------------------</td>
<td>--------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lithium Augmentation</td>
<td>Lithium + AD/AP combination vs. ECT (2 week treatment)</td>
<td>Unipolar &amp; bipolar (n=21)</td>
<td>Retrospective study</td>
<td>Lithium more effective in bipolar vs. unipolar (p=0.003); ECT more effective in unipolar</td>
</tr>
<tr>
<td>Price et al.</td>
<td>Lithium + AD/AP combination</td>
<td>Inpatients with refractory PMD (n=6)</td>
<td>Prospective (3 weeks)</td>
<td>Response in 50%; 2 patients had gradual improvement</td>
</tr>
</tbody>
</table>

Anton et al.\textsuperscript{35} | Nelson et al.\textsuperscript{37} | Price et al.\textsuperscript{38}
## APPENDIX II. Hamilton Rating Scale for Depression (21-Item)\textsuperscript{52,53}

<table>
<thead>
<tr>
<th>Item</th>
<th>Legend</th>
</tr>
</thead>
</table>
| 1) Depressed mood | 0 Absent  
1 These feeling states indicated only on questioning  
2 These feeling states spontaneously reported verbally  
3 Communicates feeling states nonverbally (ie, through facial expression, posture, voice, and tendency to weep)  
4 Subject reports virtually only these feeling states in his/her spontaneous and nonverbal communication |
| 2) Feelings of guilt | 0 Absent  
1 Self-reproach, feels he/she has let people down  
2 Ideas of guilt or rumination over past errors or sinful deeds  
3 Present illness is a punishment. Delusions of guilt  
4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations |
| 3) Suicide | 0 Absent  
1 Feels life is not worth living  
2 Wishes he were dead or any thoughts of possible death to self  
3 Suicide ideas or gestures  
4 Attempts at suicide (any serious attempt rates 4) |
| 4) Insomnia – Early | 0 No difficulty falling asleep  
1 Complains of occasional difficulty falling asleep (eg, more than 30 minutes)  
2 Complains of nightly difficulty falling asleep |
| 5) Insomnia – Middle | 0 No difficulty  
1 Complains of being restless and disturbed during the night  
2 Waking during the night – any getting out of bed rates 2 (except for purposes of voiding) |
| 6) Insomnia – Late | 0 No difficulty  
1 Waking in early hours of the morning but goes back to sleep  
2 Unable to fall asleep again if he/she gets out of bed |
| 7) Work and Activities | 0 No difficulty  
1 Thoughts and feelings of incapacity, fatigue, or weakness related to activities, work, or hobbies  
2 Loss of interest in activities, hobbies, or work – either directly reported by the subject or indirect in listlessness, indecision, and vacillation (feels has to push self to work or do activities)  
3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if subject does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores  
4 Stopped working because of present illness. In hospital, rate 4 if subject engages in no activities except ward chores, or if subject fails to perform ward chores unassisted |
| 8) Psychomotor Retardation | 0 Normal speech and thought  
1 Slight retardation at interview  
2 Obvious retardation at interview  
3 Interview difficult  
4 Complete stupor |
| 9) Psychomotor Agitation | 0 None  
1 Fidgetiness  
2 Playing with hands, hair, etc.  
3 Moving about, can’t sit still  
4 Hand wringing, nail biting, hair pulling, biting of lips |
| 10) Anxiety: Psychic | 0 No difficulty  
1 Subjective tension and irritability  
2 Worrying about minor matters  
3 Apprehensive attitude apparent in face or speech  
4 Fears expressed without questioning |
| 11) Anxiety: Somatic | 0 Absent  
1 Mild  
2 Moderate  
3 Severe  
4 Incapacitating |
| 12) Somatic Symptoms (GI) | 0 None  
1 Loss of appetite but eating without staff encouragement  
2 Difficulty eating without staff urging. Request or requires laxatives or medications for bowels or medication for GI symptoms. |
| 13) Somatic Symptoms (general) | 0 None  
1 Heaviness in limbs, back, or head. Backaches, headache, muscle aches. Loss of energy and fatigability  
2 Any clear-cut symptom rates 2 |
<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>14) Genital Symptoms</td>
<td>0: Absent, 1: Mild, 2: Severe</td>
</tr>
<tr>
<td>15) Hypochondriasis</td>
<td>0: Not present, 1: Self-absorption (bodily), 2: Preoccupation with health, 3: Frequent complaints, requests for help, etc., 4: Hypochondrial delusions</td>
</tr>
<tr>
<td>16) Loss of Weight</td>
<td>0: No weight loss, 1: Probable weight loss associated with present illness, 2: Definite (according to subject) weight loss</td>
</tr>
<tr>
<td>17) Insight</td>
<td>0: Acknowledges being depressed and ill, 1: Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc., 2: Denies being ill at all</td>
</tr>
<tr>
<td>18) Paranoid Symptoms</td>
<td>0: None, 1: Suspicious, 2: Ideas of reference, 3: Delusions of reference and persecution</td>
</tr>
<tr>
<td>19) Diurnal Variation</td>
<td>0: No variation, 1: Worse in the A.M., 2: Worse in the P.M.</td>
</tr>
<tr>
<td>20) Depersonalization &amp; Derealization (such as feelings of unreality or nihilistic ideas)</td>
<td>0: Absent, 1: Mild, 2: Moderate, 3: Severe, 4: Incapacitating</td>
</tr>
<tr>
<td>21) Obsessive &amp; Compulsive Symptoms</td>
<td>0: Absent, 1: Mild, 2: Severe</td>
</tr>
</tbody>
</table>

*HAMD-24 includes additional items assessing helplessness, hopelessness & worthlessness

<table>
<thead>
<tr>
<th>Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7</td>
<td>Normal</td>
</tr>
<tr>
<td>8-13</td>
<td>Mild Depression</td>
</tr>
<tr>
<td>14-18</td>
<td>Moderate Depression</td>
</tr>
<tr>
<td>19-22</td>
<td>Severe Depression</td>
</tr>
<tr>
<td>≥23</td>
<td>Very Severe Depression</td>
</tr>
</tbody>
</table>

APPENDIX III. Brief Psychiatric Rating Scale (BPRS)\(^53,54\)

\(^0= not assessed, 1= not present, 2= very mild, 3= mild, 4= moderate, 5= moderately severe, 6= severe, 7= extremely severe\)

1. Somatic Concern: preoccupation with physical health, fear of physical illness, hypochondriasis
2. Anxiety: worry, fear, over-concern for present or future, uneasiness
3. Emotional Withdrawal: lack of spontaneous interaction, isolation deficiency in relating to others
4. Conceptual Disorganization: lack of spontaneous interaction, isolation deficiency in relating to others
5. Guilt Feelings: Self-blame, shame, remorse for past behavior
6. Tension: Physical and motor manifestations of nervousness, over-activation
7. Mannerisms & Posturing: peculiar, bizarre, unnatural motor behavior (not including tic)
8. Grandiosity: exaggerated self-opinion, arrogance, conviction of unusual power or abilities
9. Depressive Mood: sorrow, sadness, despondency, pessimism
10. Hostility: animosity, contempt, belligerence, disdain for others
11. Suspiciousness: mistrust, belief others harbor malicious or discriminatory intent
12. Hallucinatory Behavior: perceptions without normal external stimulus correspondence
13. Motor Retardation: slowed, weakened movements or speech, reduced body tone
14. Uncooperativeness: resistance, guardedness, rejection of authority
15. Unusual Thought Content: unusual, odd, strange, bizarre thought content
16. Blunted Affect: reduced emotional tone, reduction in formal intensity of feelings, flatness
17. Excitement: heightened emotional tone, agitation, increased reactivity
18. Disorientation: confusion or lack of proper association for person, place or time

\(^a= component of BPRS Positive Symptom Subscale (BPRS-PSS)\)