Pharmacological treatment of unipolar depressive disorder

WFSBP 2015, Athens

Michael Bauer, MD, PhD
Professor and Chair of Psychiatry
University Hospital Carl Gustav Carus
Technische Universität Dresden
Germany
Major depression: common treatment options

- **Pharmacotherapy**
  - Antidepressants
  - Atypical antipsychotics & mood stabilizers
  - others: hormones (thyroid), stimulants, benzodiazepines

- **Psychological therapies**
  - Psychotherapy (cognitive-behavioral, IPT, CBASP)
  - Psychoeducation

- **Other biological treatments**
  - Brain stimulation (ECT, DBS, VNS and others)
  - Light therapy

- **Various**
  - Physical exercise (sport)
  - Social interventions
Phases of Disease and Treatment

Adapted version, original from Kupfer 1991

WFSBP Treatment Guidelines Major Depressive Disorder, Bauer et al., World Journal of Biological Psychiatry, 2013
First-line treatment of MDD

- Consensus across international guidelines: 1\textsuperscript{st} line treatment should consist of an antidepressant
  - **SSRIs**: (es)citalopram, sertraline, paroxetine, fluoxetine
  - **SNRIs**: venlafaxine, duloxetine, milnacipran
  - **Noradrenaline-serotonin modulator**: mirtazapine
  - **Noradrenaline-dopamine reuptake inhibitor**: bupropion

- Treatment preference and frequency of prescribing vary between countries

- High rates (>50\%) of insufficient response with 1\textsuperscript{st} line treatment

CANMAT, Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments; APA, American Psychiatric Association; WFSBP, World Federation of Societies of Biological Psychiatry; NICE, National Institute of Clinical Excellence; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin noradrenaline reuptake inhibitor
Limited treatment outcomes in depression (MDD)

- Moderate efficacy of antidepressants
- Results may be compromised by steady increase in placebo response rates and site numbers in trials
- Superiority of antidepressants over placebo has declined in recent years
- Recommend improved quality control of trial methods

Undurraga & Baldessarini 2012
Limited treatment outcomes in MDD

30-year meta-analytic review

- Moderate efficacy of antidepressants
- Results may be compromised by steady increase in placebo response rates and site numbers in trials
- Superiority of antidepressants over placebo has declined in recent years
- Recommend improved quality control of trial methods
- Heterogeneity of populations and trial methods limit value of meta-analysis

Undurraga & Baldessarini 2012
Outcomes in depressed outpatients requiring one or several treatment steps (STAR*D)

Up to 60% of patients do not achieve disease remission

‘Greater illness burden (ie depression chronicity, psychiatric or general medical comorbidity) was characteristic of those who required more treatment steps’

STAR*D, Sequenced Treatment Alternatives to Relieve Depression

Rush et al 2006
Suboptimal treatment responses: non-responders in STAR*D

- Approximately 50% of patients did not respond to first-line antidepressant treatment (Step 1)
- At each subsequent step, the proportion of patients who responded to treatment decreased

Response defined as ≥50% reduction in Quick Inventory of Depressive Symptomatology-Self-Report score

Rush et al 2006
Treatment goal in major depression: remission

Remission

- Minimal to No Symptoms\(^1\)
  \[ \text{HAM-D}_{17} \leq 7 \]
  \[ \text{MADRS} \leq 10 \]
- Minimise Relapse\(^3\)
- Function Restored\(^4\)

\[ \text{HAM-D}_{17} = \text{Hamilton Depression Scale}; \text{MADRS} = \text{Montgomery-Asberg Depression Rating Scale} \]

Residual symptoms predict negative outcome in depression


Survival Distribution Function = Cumulative proportion of cases surviving to given time interval

<table>
<thead>
<tr>
<th>Recovery With</th>
<th>Previous Episodes</th>
<th>n</th>
<th>Median Weeks Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>no symptoms</td>
<td>1–3</td>
<td>121</td>
<td>224</td>
</tr>
<tr>
<td>no symptoms</td>
<td>3+</td>
<td>34</td>
<td>79</td>
</tr>
<tr>
<td>1+ mild symptoms</td>
<td>1–3</td>
<td>57</td>
<td>34</td>
</tr>
<tr>
<td>1+ mild symptoms</td>
<td>3+</td>
<td>25</td>
<td>28</td>
</tr>
</tbody>
</table>
Antidepressant response: inadequate responders – definition and prediction
## Staging of treatment-resistant depression

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Failure of at least one adequate trial of one major class of AD</td>
</tr>
<tr>
<td>Stage II</td>
<td>Stage I resistance plus failure of adequate trial of AD in distinctly different class from that used in Stage I</td>
</tr>
<tr>
<td>Stage III</td>
<td>Stage II resistance plus failure of an adequate trial of TCA</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Stage III resistance plus failure of an adequate trial of MAOI</td>
</tr>
<tr>
<td>Stage V</td>
<td>Stage IV resistance plus failure of a course of bilateral ECT</td>
</tr>
</tbody>
</table>

Thase & Rush 1997
## Clinical factors associated with treatment-resistant depression

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Second step backward-elimination logistic regression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>1 Comorbid anxiety disorder</td>
<td>&lt;0.0001</td>
<td>4.2</td>
</tr>
<tr>
<td>2 Current suicidal risk</td>
<td>0.004</td>
<td>2.6</td>
</tr>
<tr>
<td>3 Melancholic features</td>
<td>0.017</td>
<td>2.3</td>
</tr>
<tr>
<td>4 Non-response to first AD treatment lifetime</td>
<td>0.012</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Non-resistance, n=346; resistance, n=356

Souery et al 2007
MDD with Anxious Distress

- Antidepressant treatments lack specificity, considered to be a main cause for low response and remission rates in MDD

- MDD with anxious distress is a specific subpopulation with high unmet need:
  - Highly prevalent (>50% of the MDD population suffers significant concurrent anxious symptoms) \( \text{(Fava et al., 2008; Weithoff et al., 2010)} \)
  - Readily recognized by clinicians in practice
  - Diagnosis is recognized in the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) classification

“The addition of an anxiety severity dimension may increase clinical awareness and increase the focus of treatment on the severity of co-morbid anxiety as a part of treatment planning, and possibly to the development of more effective treatments for co-morbid anxiety in the mood disorders and perhaps other disorders.”

DSM-5 Work Group
Patients with anxious depression (vs. non-anxious depression):

- have an earlier age of onset \(^1,^2\)
- experience a more persistent course (more and longer depressive episodes) \(^3\)
- are more severely depressed \(^5,^6\)
- have an increased risk of suicidal ideation and suicidal behavior \(^7,^8\)
- report poorer quality of life and role functioning, and overall greater functional impairment \(^5,^9\)
- incur greater personal and socioeconomic costs \(^8,^{10-12}\)

Trajectory of illness differs

\(^1\) Seo et al., 2011; \(^2\) Lamers et al., 2011; \(^3\) Pennix et al., 2011; \(^4\) Coryell et al., 2012; \(^5\) Fava et al., 2008; \(^6\) Wiethoff et al., 2010; \(^7\) Fava et al., 2004; \(^8\) Sareen et al., 2005; \(^9\) Wittchen et al., 2000; \(^10\) Stein, 2001; \(^11\) Wittchen et al., 1994; \(^12\) Hoffman et al., 2008
• **Presence of significant anxiety symptoms is a negative predictor for treatment outcomes in MDD** as well as a negative moderator of treatment response
  
  – Higher rates of treatment failure, lower remission rates *(Fava et al., 2008; Souery et al., 2007)*

  Treatment response differs

• **No specific antidepressant treatment for this subpopulation**
  
  – High level of dissatisfaction with current monotherapy approaches
  
  – Frequent polypharmacy (addition to SSRI/SNRI):
    – benzodiazepines
    – atypical antipsychotic
    – mood stabilizer

  • Side effect burden/safety issues with all of these approaches limit their utility, especially in long term use

  Significant unmet need
Citalopram Response in STAR*D: Anxious vs. Non-Anxious MDD

Remission Rate

Remission Rates (HAM-D-17 < 8) in Level 2 of STAR*D: Anxious vs. Non-Anxious MDD

* p<.05

Time to remission: better outcome in non-anxious depression vs. anxious depression
(Cox regression analysis)

MDD with anxious features as a target indication

Summary:
- Well-established, well-recognized, clinically relevant subtype of MDD
- Trajectory of illness differs from non-anxious depressed patients (more severe, persistent, higher suicide risk)
- Response to currently available antidepressants differs from non-anxious depressed patients (lower remission rates, more residual symptoms, higher relapse risk, greater chronicity of illness)
- Recognition within the DSM-5 with the addition of the anxious distress specifier to the MDD diagnostic criteria, with no requirement to exclude GAD

“The addition of an anxiety severity dimension may increase clinical awareness and increase the focus of treatment on the severity of co-morbid anxiety as a part of treatment planning, and possibly to the development of more effective treatments for co-morbid anxiety in the mood disorders and perhaps other disorders.”

Mood Disorders Work Group, DSM-5
American Psychiatric Association
Treatment patterns following an inadequate response to first-line antidepressant treatment

- Switching antidepressant: 39.6%
- Augmentation: 17.9%
- Combination: 23.8%
- Mixed: 18.8%

n=336. Non-interventional study conducted in 60 community mental health centres in Spain

Garcia-Toro et al 2012
<table>
<thead>
<tr>
<th></th>
<th>Switching</th>
<th>Combination</th>
<th>Augmentation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of previous episodes, mean</td>
<td>1.8</td>
<td>2.0</td>
<td>3.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Previous hospitalisation, %</td>
<td>9.0</td>
<td>12.5</td>
<td>25.0</td>
<td>13.6</td>
</tr>
<tr>
<td>Previous suicide attempt, %</td>
<td>15.2</td>
<td>21.3</td>
<td>26.7</td>
<td>19.5</td>
</tr>
<tr>
<td>Family history of psychiatric disorders, %</td>
<td>42.1</td>
<td>55.0</td>
<td>50.0</td>
<td>47.6</td>
</tr>
<tr>
<td>Duration (weeks) of AD treatment, mean</td>
<td>12.7</td>
<td>10.6</td>
<td>12.2</td>
<td>12.0</td>
</tr>
<tr>
<td>Presence of psychotic symptoms, %</td>
<td>2.3</td>
<td>6.3</td>
<td>18.3</td>
<td>7.0</td>
</tr>
<tr>
<td>MADRS total score, mean</td>
<td>31.5</td>
<td>32.5</td>
<td>32.8</td>
<td>32.1</td>
</tr>
<tr>
<td>MADRS Item 10 (suicidality) score, mean</td>
<td>2.0</td>
<td>2.3</td>
<td>2.5</td>
<td>2.2</td>
</tr>
<tr>
<td>HAM-A total score, mean</td>
<td>24.3</td>
<td>24.0</td>
<td>23.0</td>
<td>24.0</td>
</tr>
<tr>
<td>CGI-S score, mean</td>
<td>4.5</td>
<td>4.7</td>
<td>4.7</td>
<td>4.6</td>
</tr>
</tbody>
</table>

n=336. Non-interventional study conducted in 60 community mental health centres in Spain
CGI-S, Clinical Global Impression-Severity; HAM-A, Hamilton anxiety Rating Scale
MADRS, Montgomery Åsberg Depression Rating Scale

Garcia-Toro et al 2012
Treatment strategies for refractory depression

What do evidence-based treatment guidelines recommend?
REVIEW ARTICLE

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders

MICHAEL BAUER1, ANDREA PFENNIG1, EMANUEL SEVERUS1, PETER C. WHYBROW2, JULES ANGST3, HANS-JÜRGEN MÖLLER4, 
& Task Force on Unipolar Depressive Disorders*

1Department of Psychiatry and Psychotherapy, Carl Gustav Carus University Hospital, Technische Universität Dresden, Dresden, Germany, 2Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior Los Angeles, University of California Los Angeles (UCLA), Los Angeles, CA, USA, 3Department of Psychiatry, University of Zürich, Zürich, Switzerland, and 4Department of Psychiatry, University of Munich, Munich, Germany

*Michael Bauer, Germany (Chair), Jules Angst, Switzerland (Co-Chair), Andrea Pfennig and Emanuel Severus, Germany (Secretary), Mazda Adli (Germany), Ian Anderson (UK), José L. Ayuso-Gutierrez (Spain), David Baldwin (UK), Per Bech (Denmark), Otto Benkert (Germany), Michael Berk (Australia), Istvan Bitter (Hungary), Tom Bisch (Germany), Graham Barrows (Australia), Giovanni Cassano (Italy), Marcelo Cetkovich-Bakmas (Argentina), John C. Cookson (UK), Delcel da Costa (Brazil), Mihai D. Gheorghe (Romania), Heinz Grunze (UK), Gerardo Heinz (Mexico), Teruhiko Higuchi (Japan), Robert M.A. Hirschfeld (USA), György Höschl (Czech Republic), Edith Höflebinder-Trachsel (Switzerland), Heon-Hui Kang (Korea), Siegfried Kasper (Austria), Cornelius Katona (UK), Martin B. Keller (USA), Selcuk Kirli (Turkey), E. Kostyukova (Russia), Parmeendiar Kuthara (United Arab Emirates), David J. Kupfer (USA), Min-Soo Lee (Korea), Brian Leonard (Ireland), Rasnus W. Licht (Denmark), Se-Won, Lim (Korea), Odd Lingjaerde (Norway), Chia-Yih Liu (Taiwan), Henrik Lutken (Denmark), Julien Mendlowitz (Belgium), Philip B. Mitchell (Australia), Hans-Jürgen Möller (Germany), Jong-Woo Paik (Korea), Yong Chon Park (Korea), Eugene S. Perry (UK), Stanislaw Puzynski (Poland), A. John Rush (USA), Janusz K. Rybakowski (Poland), Isaac Schweitzer (Australia), Andre Tadic (Germany), Andre Tylee (UK), Jürgen Unützer (USA), Per Vestergaard (Denmark), Eduard Vieta (Spain), Peter C. Whybrow (USA), Kazuo Yamada (Japan), Aylin Yazici (Turkey).

Correspondence: Michael Bauer, M.D., Ph.D., Professor of Psychiatry, Department of Psychiatry and Psychotherapy, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Fetscherstr. 74, D-01307 Dresden, Germany. Tel: +49 351 4582772. Fax: +49 351 4584324. E-mail: michael.bauer@uniklinikum-dresden.de

WFSBP Treatment Guidelines Major Depressive Disorder, Bauer et al., World Journal of Biological Psychiatry, 2013
Strategies for addressing a suboptimal treatment response in MDD

- Increasing dose\textsuperscript{1-5}
- Switching antidepressants\textsuperscript{1-6}
- Augmentation with:
  - lithium\textsuperscript{1-6}
  - atypical antipsychotics\textsuperscript{1-4,6}
  - triiodothyronine (T3) or thyroxine (T4)\textsuperscript{1,3,4}
- Addition of psychotherapy\textsuperscript{1-5}

\textsuperscript{1}Bauer et al 2013, WFSBP; \textsuperscript{2}NICE 2010; \textsuperscript{3}APA 2010; \textsuperscript{4}CANMAT 2009
\textsuperscript{5}S3-Guideline / National Disease Management (German) Guideline 2011; \textsuperscript{6}Connolly & Thase 2011
Partial or non-response to 2–4 week treatment with an antidepressant at adequate dosage

Consider treatment optimisation (dose increase)

Combining two antidepressants from different classes

Augmentation strategies: adding a second non-antidepressant drug

Switch to a new antidepressant from a different or same pharmacological class

Consider adding psychotherapy at any time during treatment

Consider ECT at any time during treatment

Adapted from Bauer et al 2007, World Federation of Societies of Biological Psychiatry (WFSBP)
Treatment strategies for depression: WFSBP guidelines

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Adapted from Bauer et al 2007, World Federation of Societies of Biological Psychiatry (WFSBP)
Step 1: Optimize treatment

- Compliance? Make sure patient takes the medication

- Make sure you do not oversee facts that keeps the patient in depression
  - Psychiatric comorbidity (e.g. alcohol or dependency)
  - Medical comorbidity (e.g. thyroid dysfunction)
  - Psychosocial stressors (e.g., conflict with partner or job)

- Consider TDM and genotyping (CYP inhibitors)

- Consider antidepressant dose increase?
NICE guidelines for treatment following inadequate response to AD

- Check adherence and side effects
- Switch AD
  - different SSRI or better-tolerated AD
  - antidepressant of different class, a TCA or MAOI
- Caution when switching – interactions
- Augmenting ADs
  - lithium
  - antipsychotic (eg aripiprazole, olanzapine, quetiapine XR, risperidone)
  - another AD (eg mianserin, mirtazapine)

NICE 2009
Dose escalation: the evidence

Clinical guidelines state that optimising antidepressant dose and duration should be considered before deciding that treatment has failed.

Systematic review of antidepressant dose escalation after failure of medium-dose treatment concluded...

High-dose TCAs & venlafaxine recommended in patients not responding to medium-dose therapies.

High-dose SSRIs not recommended in patients not responding to medium-dose SSRIs.

Adli et al 2005; Connolly & Thase 2011
High-dose SSRI (paroxetine) is not effective in MDD

Randomisation of non-responders

Paroxetine (20 mg) 6 weeks

Paroxetine DE 6 weeks

Placebo DE 6 weeks

Inclusion

Clinical visits, questionnaire measurements

Baseline SPECT

Second SPECT

Third SPECT

Week: -6 -4 -2 0 1 2 4 6 T0 T1

Entry

SPECT measurements showed no significant differences in midbrain SERT occupancy between paroxetine DE and placebo DE

DE, dose escalation; SERT, serotonin transporter
SPECT, single-photon emission computed tomography

Rühé et al 2009
High-dose SSRI (paroxetine) is not effective in MDD

*"p<0.05 for placebo DE vs paroxetine DE
Nonpsychotic outpatients with MDD; change over time in Maier and IDS-SR scores (n=57)
Maier score, Maier and Bech 6-item subscale of the HAM-D_{17}
DE, dose escalation; IDS-SR, Inventory for Depressive Symptomatology-Self-rated
Ruhé et al 2009
Switching the antidepressant
When to change strategy?

- Traditional belief: antidepressant response usually appears with a delay of several weeks.
- Most placebo-controlled trials do not show a significant effect of treatment before Week 3.
- Most treatment guidelines are still reflective of this, and suggest that treatment should only be changed if a partial response has not occurred after 4-6 weeks.
Predictive value of early improvement and early non-improvement

Meta-analysis: 41 studies with TCAs, mirtazapine, SSRIs, venlafaxine, etc. 
(n=6562)

6562 patients with MDD from 41 studies

Week 2

35% of patients did not achieve a 20% reduction of HAM-D\textsubscript{17}

Weeks 4-8

Of this 35%, only 4% had achieved remission at Weeks 4-8

Lack of improvement during the first 2 weeks of treatment may indicate that changes in depression management should be considered earlier than conventionally thought

Szegedi et al 2009
CANMAT: algorithm for patients who do not achieve 20% symptom reduction within 1-4 weeks

- **Start and optimise first-line antidepressant**
- **Evaluate patient improvement using rating scales**
- **No improvement (<20% change) or patient intolerant → evaluate side effects and residual symptoms**
- **Switch to a new antidepressant with evidence for efficacy**
- **Treat the patient to remission**
- **Evaluate risk factors for relapse**

**Maintenance treatment**

Lam et al 2009
Partial or non-response to 2–4 week treatment with an antidepressant at adequate dosage

Consider treatment optimisation (dose increase)

Combining two antidepressants from different classes (level C)

Augmentation strategies (level A, B and C)

Switch to a new antidepressant from a different or same pharmacological class (level B)

Consider adding psychotherapy at any time during treatment

Consider ECT at any time during treatment

Adapted from Bauer et al 2007, World Federation of Societies of Biological Psychiatry (WFSBP)
German Step-3 evidence and consensus-based guidelines for MDD

Dosiserhöhung bei Verträglichkeit
- Bei TZA oder Venlafaxin
- Im Rahmen der Anwendungsempfehlung
- Nicht bei SSRI

Ansprechen?
- Ja
  - Erhaltungstherapie
- Nein
  - Wechsel des Antidepressivums

Lithiumaugmentation
- 2 Wochen mit Lithiumspiegel im therapeutischen Bereich

Ansprechen?
- Ja
  - Erhaltungstherapie
- Nein
  - Antidepressiva-Kombination

Check
- Psychotherapie (4.4)
- Somatische, nichtmedikamentöse Verfahren (4.5)

DGPPN et al. 2009
Benefits and limitations of strategies for treatment-resistant MDD

**Switching**

**Advantages**
- Avoids polypharmacy
- Potential AE range smaller
- Lower costs

**Disadvantages**
- Possible loss of partial response from initial treatment
- Limited effectiveness of monotherapies

**Adjunct/Combination**

**Advantages**
- Adds to achieved symptom improvement with initial antidepressant

**Disadvantages**
- Multiple drugs
- Potential AE range greater
- Higher costs

Shelton et al 2010
Meta analysis of switching AD versus continuation with index AD

Response rates

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Switch n/N</th>
<th>Continuation n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferreri et al</td>
<td>16/33</td>
<td>14/38</td>
<td>14.66 1.61 (0.62, 4.17)</td>
<td>100.00</td>
<td>0.85 (0.55, 1.30)</td>
<td>2001</td>
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<tr>
<td>Shelton et al</td>
<td>41/142</td>
<td>21/68</td>
<td>44.17 0.91 (0.48, 1.71)</td>
<td></td>
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<td>2005</td>
</tr>
<tr>
<td>Corya et al</td>
<td>19/56</td>
<td>29/58</td>
<td>41.17 0.51 (0.24, 1.09)</td>
<td></td>
<td></td>
<td>2006</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>231</td>
<td>164</td>
<td></td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 78 (switch), 64 (continuation)
Test for heterogeneity:
\( \chi^2 = 3.50, df=2 \) (p=0.17), p=42.9%
Test for overall effect: \( Z = 0.75 \) (p=0.45)

Meta analysis of three double-blind studies in patients with MDD and inadequate response to index AD who were subsequently randomised to switch ADs or to continue with index AD (n=395)

Bschor & Baethge 2010
In this meta-analysis, higher rates of remission were associated with switching to a non-SSRI.

†Rush et al (2006): top box represents sertraline-venlafaxine pair-wise comparison; bottom box represents sertraline-bupropion pair-wise comparison
Switching doesn’t offer benefits over continuation

- Meta-analysis suggests no benefit in response rates and marginal benefit in remission rates of switching from one class of AD to another \(^1\)
- Several studies report no advantage to switching to another antidepressant class \(^2\text{-}^4\)
- Response rates following *within class* switches are low, although variable: TCAs 9-30\%, SSRIs 27-72\% \(^1\)
- No advantage was seen for switching versus continuing in a systematic meta-analysis.\(^3\) A recent, carefully designed study confirmed these findings, with continuation with the same treatment associated with a higher remission rate than switching to another class \(^5\)

\(^1\) Ruhe et al., 2006; \(^2\) Rush et al., 2006; \(^3\) Bschor and Baethge 2010, \(^4\) Souery et al., 2011a; \(^5\) Souery et al., 2011b
Combination of antidepressant medications is among the most commonly used treatment strategies in major depressive disorder.

Justified by data?
Treatment strategies for depression: WFSBP guidelines

Partial or non-response to 2- to 4-week treatment with an antidepressant at adequate dosage

Consider treatment optimisation eg dose escalation

Combination strategy: combine two antidepressants from different classes

Augmentation strategy: add a non-antidepressant agent

Switch to a new antidepressant from a different or same pharmacological class

Consider adding psychotherapy at any time during treatment

Consider ECT at any time during treatment

WFSBP, World Federation of Societies of Biological Psychiatry
Indications for combined use of antidepressants in MDD

- Adding a second antidepressant in partial responders or non-responders to an antidepressant

- Two antidepressants from the beginning of treatment to enhance outcome
  - more rapid onset of therapeutic action or
  - greater efficacy
Potentially effective and safe combinations of antidepressants in MDD

- **SSRI plus**
  - Bupropion
  - Mirtazapine / Mianserine
  - TCA / tetracyclics

- **TCA plus**
  - SSRI / SNRI
  - Bupropion
  - Mirtazapine / Mianserine
  - Tetracyclics

- **SNRI plus**
  - Bupropion
  - Mirtazapine / Mianserine
  - TCA / tetracyclics

- **Mirtazapine / Mianserine plus**
  - Bupropion
  - SSRI / SNRI
  - TCA / tetracyclics
Combination of an SSRI with an inhibitor of presynaptic autoreceptors (e.g., mirtazapine) is an evidence-based choice in cases where monotherapy failed. The combination of venlafaxine with mirtazapine may be accompanied by worsening side effects.

CE A, RG 2
But - Cautious use of some antidepressant combination in MDD

- Irreversible MAO inhibitors (phenelzine, tranylcypromine) should not be added to serotonergic drugs, e.g.
  - SSRI
  - SNRI
  - Clomipramine
- and vice versa
- Risk of serotonin syndrome
Combination of Antidepressant Medications From Treatment Initiation for Major Depressive Disorder

- Two different antidepressants from the beginning of treatment to enhance outcome
- 2 recent large-scale controlled studies:
  - Blier et al. 2010
  - Rush et al. 2011
Combination of Antidepressant Medications From Treatment Initiation for Major Depressive Disorder: A Double-Blind Randomized Study

FIGURE 1. Mean Scores on the Hamilton Depression Rating Scale (HAM-D), by Visit, for All Patients Treated (Last Observation Carried Forward) in a Randomized Trial of Antidepressant Monotherapy or Combination Treatment.

Combining Medications to Enhance Depression Outcomes (CO-MED): Acute and Long-Term Outcomes of a Single-Blind Randomized Study

Recruitment and Treatment of Depressed Patients in a Comparison of Antidepressant Monotherapy With Two Antidepressant Combinations

Rush et al. (2011) Am J Psychiatry
Combining Medications to Enhance Depression Outcomes (CO-MED): Acute and Long-Term Outcomes of a Single-Blind Randomized Study

Rates of Remission and Response for Depressed Patients in a Comparison of Antidepressant Monotherapy With Two Antidepressant Combinations

Remission was defined as scores of less than 8 and less than 6 on the 16-item Quick Inventory of Depressive Symptomatology—Self-Report (QIDS-SR) (29) at the last two consecutive assessments. Response was defined as a reduction of at least 50% in QIDS-SR score.

Rush et al. (2011) Am J Psychiatry
Partial or non-response to 2- to 4-week treatment with an antidepressant at adequate dosage

Consider treatment optimisation eg dose escalation

Combination strategy: combine two antidepressants from different classes

Augmentation strategy: add a non-antidepressant agent

Switch to a new antidepressant from a different or same pharmacological class

Consider adding psychotherapy at any time during treatment

Consider ECT at any time during treatment
Most commonly used augmentation strategies in depression

- Lithium
- Atypical antipsychotic
- Thyroid hormone
- Anticonvulsants
- Others (Psychotherapy)
- Stimulant
Augmentation with lithium, antipsychotics – or others?

What first and what's the best evidenced?
Augmentation Strategies for Refractory Depression

Evidence-Level

- **Lithium** A
- **Atypical antipsychotics** A/B/C
  - Aripiprazole, Quetiapine A
- **Triiodothyronine (T3)** B
- **L-Thyroxine** C
- **Buspirone** C
- **Anticonvulsants** C
- **Estrogen** C
- **Dopaminagonists** C
- **Psychostimulants** C

### Meta-Analysis: Lithium Augmentation in Refractory Depression (10 RCTs)

<table>
<thead>
<tr>
<th>Study</th>
<th>Lithium n/N</th>
<th>Control n/N</th>
<th>OR (fixed) 95% CI</th>
<th>OR (fixed) 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henninger</td>
<td>5/8</td>
<td>0/7</td>
<td>23.57 [1.00, 556.08]</td>
<td></td>
<td>1983</td>
</tr>
<tr>
<td>Kantor</td>
<td>1/4</td>
<td>0/3</td>
<td>3.00 [0.09, 102.05]</td>
<td></td>
<td>1986</td>
</tr>
<tr>
<td>Zusty</td>
<td>3/8</td>
<td>2/8</td>
<td>1.80 [0.21, 15.41]</td>
<td></td>
<td>1988</td>
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<tr>
<td>Schoepf</td>
<td>7/14</td>
<td>0/13</td>
<td>27.00 [1.35, 541.57]</td>
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<td>1989</td>
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<tr>
<td>Browne</td>
<td>3/7</td>
<td>2/10</td>
<td>3.00 [0.35, 25.87]</td>
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<td>1990</td>
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<tr>
<td>Joffe</td>
<td>9/17</td>
<td>3/16</td>
<td>4.88 [1.01, 23.57]</td>
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<td>1993</td>
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<tr>
<td>Stein</td>
<td>2/16</td>
<td>4/18</td>
<td>0.50 [0.08, 3.19]</td>
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<td>1993</td>
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<tr>
<td>Katona</td>
<td>15/29</td>
<td>8/32</td>
<td>3.21 [1.09, 9.48]</td>
<td></td>
<td>1994</td>
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<tr>
<td>Baumann</td>
<td>6/10</td>
<td>2/14</td>
<td>9.00 [1.27, 63.89]</td>
<td></td>
<td>1996</td>
</tr>
<tr>
<td>Nierenberg</td>
<td>2/18</td>
<td>3/17</td>
<td>0.58 [0.08, 4.01]</td>
<td></td>
<td>2003</td>
</tr>
</tbody>
</table>

Total (95% CI): 131/138

Test for heterogeneity: $\chi^2 = 11.90$, df = 9 (P = 0.22), I² = 24.4%

Test for overall effect: $z = 4.06$ (P < 0.0001)

Meta-analysis of 10 Placebo-RCTs
lithium augmentation vs placebo

Response (%): 45

Lithium: *p < 0.001
NNT=5

Placebo: n=269

Which patients are prime candidates for lithium augmentation?

- Patients with high number of recurrences and indication for relapse prevention (long-term treatment)
- Patients with endogenous (melancholic) features
- Patients with suicidality (lithium has anti-suicide activity)

Augmentation with Antipsychotics
Antipsychotics (neuroleptics) in augmentation therapy of depression

- No placebo-controlled studies (RCT) with typical (classic) neuroleptics (e.g., haloperidol)
- Atypical antipsychotics: in recent years, several RCTs
- Aripiprazole, risperidone, olanzapine (as OFC) and quetiapine XR have demonstrated efficacy as adjunct therapy in patients with an inadequate response to antidepressants
Aripiprazole adjunct therapy in patients with MDD and inadequate response to antidepressant

MADRS total score

Mean change from baseline in MADRS total score

Week

0 1 2 3 4 5 6

-12 -10 -8 -6 -4 -2 0

Placebo + AD (n=169)
Aripiprazole + AD (n=174)

Placebo + AD (n=184)
Aripiprazole + AD (n=185)

Placebo + AD (n=172)
Aripiprazole + AD (n=181)

* p<0.05; ** p<0.01; *** p≤0.001 vs placebo + AD (LOCF)

Patients had history of inadequate response to ADs plus an 8-week prospective failure on AD monotherapy

AD, antidepressant

Berman et al. CNS Spectr 2009;14:197
Adjunctive quetiapine XR in patients with MDD and inadequate response to antidepressant

El-Khalili et al. *Int J Neuropsychopharmacol* 2010;13:917

LSM change from baseline in MADRS total score

**Placebo + AD (n=143)**
**QTP XR 150 mg + AD (n=143)**
**QTP XR 300 mg + AD (n=166)**

* *p<0.05; **p<0.01; ***p<0.001 vs placebo + AD (MITT; LOCF)

Patients with an inadequate response to AD during current episode
Comparator augmentation studies
RUBY: study design
open-label, rater-blinded

14-day enrolment period
Patients on SSRI/venlafaxine
and with sub-optimal response before randomisation

Add-on quetiapine XR to ongoing SSRI / venlafaxine
Quetiapine XR monotherapy
Add-on lithium to ongoing SSRI / venlafaxine

Enrolment (Day -14 to -1)
Randomisation
D1 D4 D8
D43
Treatment period (6 weeks)

Quetiapine XR titration: Day 1-2, 50 mg; Day 3-4, 150 mg; Day 5-43, 300 mg;
Lithium titration: Day 1-2, 450 mg; Day 3-43, 900 mg, with dose adjustments according to blood level

Bauer et al 2010
Quetiapine XR (adjunct/monotherapy) vs lithium + AD in treatment-resistant depression

Open-label study: MADRS total score

All p values vs lithium + AD (MITT; LOCF); significance requires p<0.025 due to multiplicity

Randomised, open-label, rater-blinded study (RUBY)

Patients with Stage I or II treatment-resistant depression and MADRS total score ≥25

Stage 1 = failure of ≥1 adequate trial of 1 major class of AD
Stage 2 = failure of adequate trials of 2 different classes of major AD

RUBY study: response and remission

Response rate

Remission rate

Add-on quetiapine XR (n=229)
Quetiapine XR monotherapy (n=225)
Add-on lithium (n=221)

MITT population

aMADRS response defined as a ≥50% reduction in total score from baseline
Levothyroxine improves mood in bipolar depression: a randomized, placebo-controlled study

Clinical Improvement during L-T4 treatment (HAMD score reduction)

Brain areas where change in relative activity after treatment was correlated with change in depressed mood (HamD17)

Systematic stepwise approaches in treating inpatients with major depression: algorithmic strategies
Strategies for the treatment of nonpsychotic MDD
(Texas Medication Algorithm Project)

Stage 1
Monotherapy
SSRI, BUP_{SR}, NEF, VLF_{XR} or MRT
Any stage(s) can be skipped depending on the clinical picture

Stage 2
Monotherapy
SSRI, BUP_{SR}, NEF, TCA, VLF_{XR} or MRT
Partial response or nonresponse

Stage 3
Monotherapy
SSRI, BUP_{SR}, NEF, TCA, VLF_{XR}, MRT, MAOI
From a class other than used in stage 1 or 2

Stage 4
Monotherapy
SSRI, BUP_{SR}, NEF, TCA, VLF_{XR}, MRT, MAOI
From a class other than used in stage 1 or 2

Stage 5
Combination antidepressants:
• TCA + SSRI
• NEF + SSRI
• BUP_{SR} + SSRI
• BUP_{SR} + NEF

Stage 6
Lithium augmentation

Stage 7
Combination antidepressants:
• TCA + SSRI
• NEF + SSRI
• BUP_{SR} + SSRI
• BUP_{SR} + NEF

Maintenance phase when indicated

• TCA + SSRI
• NEF + SSRI
• BUP_{SR} + SSRI
• BUP_{SR} + NEF

BUP_{SR}, bupropion sustained release; ECT, electroconvulsive therapy; fluox, fluoxetine
MRT, mirtazapine; NEF, nefazodone; SSRI, selective serotonin reuptake inhibitor
TCA, tricyclic antidepressants; VLF_{XR}, venlafaxine extended release

Trivedi et al 2004
Texas Medication Algorithm Project: depression outcomes

Adjusted mean symptoms for all patients according to the IDS-C₃₀ during 12-month ALGO compared with TAU (N=350)

IDS-C₃₀ total score

Baseline 1 2 3 4

TAU (n=175) ALGO (n=175)

IDS-C₃₀, 30-item Inventory of Depressive Symptomatology-Clinician-rated scale

Trivedi et al 2004
Algorithm (ALGO) flow chart

Excluding diagnoses
- Schizoaffective disorder
- Drug dependency
- Alcohol dependency
- Personality disorders
- Organic brain disorders

Admission diagnosis: depressive syndrome
- Verify diagnosis (ICD-10)

Steps 1 + 2
- Taper previous, unsuccessful medication
- Exclude organic disorders
- Further diagnostic evaluation
- Sleep deprivation

Steps 3 + 4
- Antidepressant monotherapy
  - High dose treatment after 2 weeks (if tolerable)

Assess response (BRMS)
- Remission (BRMS <8)
  - Confirm after 1 week
- No response (BRMS change <6)
  - Switch to next step
- Partial remission (BRMS change >5)
  - Remain in same step for another 2 weeks

Step 5
- Lithium augmentation

Step 6
- Lithium monotherapy

Steps 7 + 8
- Lithium + MAOI
  - Low dose
  - High dose

Steps 9 + 10
- Discontinuation + ECT

Reassess response (BRMS) and diagnosis
- Proceed to next step according to same response/reassessment criteria as after Step 1

Duration (weeks)
- 1
- 4-8
- 4-6
- 2-4
- 4-8
- 4

BRMS, Bech-Rafaelsen Melancholia Scale; MAOI, monoamine oxidase inhibitor

Bauer et al 2009
Algorithm-guided treatment (ALGO) versus treatment as usual (TAU)

Rate of non-remitted patients (%)

Time (weeks)

TAU (n=74) ALGO (n=74)

Hazard ratio=2.0; p=0.004
Survival analysis (ITT group)

Bauer et al 2009
GUIDELINES

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders. Part 2: Maintenance Treatment of Major Depressive Disorder—Update 2015

MICHAEL BAUER1, EMANUEL SEVERUS1, STEPHAN KÖHLER2, PETER C. WHYBROW3, JULES ANGST4 & HANS-JÜRGEN MÖLLER5; ON BEHALF OF THE WFSBP TASK FORCE ON TREATMENT GUIDELINES FOR UNIPOLAR DEPRESSIVE DISORDERS*

1Department of Psychiatry and Psychotherapy, TU Dresden, Germany, 2Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, Berlin, Germany, 3Semel Institute for Neuroscience and Human Behavior Los Angeles, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles (UCLA), Los Angeles, CA, USA, 4University of Zürich, Department of Psychiatry, Zürich, Switzerland, and 5University of Munich, Department of Psychiatry, Munich, Germany

Abstract
These guidelines for the treatment of unipolar depressive disorders systematically review available evidence pertaining to the biological treatment of patients with major depression and produce a series of practice recommendations that are clinically and scientifically meaningful based on the available evidence. These guidelines are intended for use by all physicians assessing and treating patients with these conditions. The relevant data have been extracted primarily from various treatment guidelines and panels for depressive disorders, as well as from meta-analyses/reviews on the efficacy of antidepressant medications and other biological treatment interventions identified by a search of the MEDLINE database and Cochrane Library. The identified literature was evaluated with respect to the strength of evidence for its efficacy and was then categorized into five levels of evidence (CE A–F) and five levels of recommendation grades (RG 1–5). This second part of the WFSBP guidelines on depressive disorders covers the management of the maintenance phase treatment, and is primarily concerned with the biological treatment (including pharmacological and hormonal medications, electroconvulsive therapy and other brain stimulation treatments) of adults and also, albeit to a lesser extent, children, adolescents and older adults.
Factors associated with increased risk for recurrence in recurrent depression

<table>
<thead>
<tr>
<th>Table II. Factors associated with increased risk for recurrence in major depressive disorder.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Three or more episodes of major depression</td>
</tr>
<tr>
<td>• High prior rate of recurrence (e.g., two episodes within 5 years)</td>
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<tr>
<td>• Previous episode in the last year</td>
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<tr>
<td>• Residual symptoms during continuation phase treatment</td>
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<tr>
<td>• Residual subsyndromal symptoms at remission</td>
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<tr>
<td>• Concurrent dysthymic disorder (“double depression”)</td>
</tr>
<tr>
<td>• Severity of episodes (includes suicidality and psychotic features)</td>
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<tr>
<td>• Longer previous episodes</td>
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<tr>
<td>• Relapse after medication withdrawal</td>
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<tr>
<td>• Concurrent coexisting substance abuse</td>
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<tr>
<td>• Concurrent coexisting anxiety disorders</td>
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<tr>
<td>• Family history of major depressive disorder in first degree relatives</td>
</tr>
<tr>
<td>• Onset prior to age 30</td>
</tr>
</tbody>
</table>

Bauer et al. World J Biol Psychiatry 2015
Relapse prevention in recurrent depression: antidepressants 1\textsuperscript{st} line *

- TCA* (AMI, IMI, NOR, DES)
- MAO-inhibitors*
- SSRIs*
- SSNRI (Venlafaxine, duloxetine) *
- Agomelatine*
- Lithium* : alternative choice (2\textsuperscript{nd} line)

* significant better than placebo in RCT

Bauer et al. World J Biol Psychiatry 2015
Relapse rates (%) after 1 and 2 years with antidepressants in recurrent depression: systematic review


Abb. 3.: Rückfallraten (%) nach 1 bzw. 2 Jahren unter Antidepressiva vs. Placebo bei Patienten, die zuvor eine 4-6-monatige Erhaltungstherapie hatten (aus verschiedenen Studien) (Geddes et al, Lancet 2003;361:653-61)
Summary

- Antidepressants are 1st line therapy for MDD, but many patients with MDD do not achieve a satisfactory outcome.
- Guidelines recommend switching, combination and augmentation strategies following an inadequate response to antidepressants.
- Adjunct therapy with lithium and some atypical antipsychotics are currently best-evidenced options for patients with inadequate response to antidepressants.
- Recent studies suggest that data from Week 2 may be a powerful predictor of eventual response / non-response.
- Algorithm-guided treatment has demonstrated improved clinical outcomes compared with treatment as usual.
Thank you for your Attention