Treatment strategies in major depression
What to use when?

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First-line treatment of MDD

- **consensus across international guidelines:** 1\(^{st}\) 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\(^{st}\) 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
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

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WFSBP Treatment Guidelines Major Depressive Disorder, Bauer et al., World Journal of Biological Psychiatry, 2013
Evidence-based classification of recommendations

According to Bandelow et al. (2008) and Grunze et al. (2009), six categories of evidence (CE A to F) were used:

CE A: Full evidence from controlled trials
CE B: Limited positive evidence from controlled trials
CE C: Evidence from uncontrolled studies or case reports/expert opinion
CE D: Inconsistent results
CE E: Negative evidence
CE F: Lack of evidence.

See Table I for details.

Recommendations were then derived from the category of evidence for efficacy (CE) and from additional aspects such as safety, tolerability, and interaction potential and where labelled 1 to 5:

RG 1: CE A evidence and good risk–benefit ratio
RG 2: CE A evidence and moderate risk–benefit ratio
RG 3: CE B evidence
RG 4: CE C evidence
RG 5: CE D evidence.

WFSBP Treatment Guidelines Major Depressive Disorder, Bauer et al., World Journal of Biological Psychiatry, 2013
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 e.g. 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

Adapted from Bauer et al, 2013
Dose escalation

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 recommended in patients refractory to medium-dose TCAs

High-dose SSRIs not recommended in patients refractory to medium-dose SSRIs

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

Randomisation of non-responders

Paroxetine (20 mg) 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

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

Ruhé 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
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
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Consider adding psychotherapy at any time during treatment

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WFSBP, World Federation of Societies of Biological Psychiatry

Adapted from Bauer et al, 2013
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</td>
<td>1.61 (0.62, 4.17)</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>Shelton et al</td>
<td>41/142</td>
<td>21/68</td>
<td>44.17</td>
<td>0.91 (0.48, 1.71)</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Corya et al</td>
<td>19/56</td>
<td>29/58</td>
<td>41.17</td>
<td>0.51 (0.24, 1.09)</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>231</td>
<td>164</td>
<td>100.00</td>
<td>0.85 (0.55, 1.30)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 78 (switch), 64 (continuation)
Test for heterogeneity: Chi²=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
Switching AD therapy in SSRI-resistant MDD: within-class vs across-class switch

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

Papakostas et al 2008
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
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
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
STAR*D Treatment Strategies and Options

LEVEL 1
- Citalopram
  - SWITCH
    - BUP-SR
    - SERT
    - VEN-XR
  - AUGMENT
    - CT
    - CT + CIT

LEVEL 2
- CIT + BUP-SR
- CIT + BUS
  - SWITCH
    - BUP-SR
    - VEN-XR
  - AUGMENT
    - Li + BUP-SR, SERT, VEN-XR, or CIT
    - T₃ + BUP-SR, SERT, VEN-XR, or CIT

LEVEL 2A
- SWITCH
  - MIRT
  - NTP

LEVEL 3
- SWITCH
  - TCP
  - MRT + VEN-XR

STAR*D Clinical Study Results
Remission Rates (HAM-D-17 < 8)

Level 1
11.9 weeks
Mono

Level 2
(1 failure)
8-10 weeks
Augm
Mono

Level 3
(2 failures)
≤ 14 weeks
Augm
Mono

Level 4
(3 failures)
≤ 14 weeks
Augm
Mono

% Remission

Treatment Resistance
Mono = monotherapy
Augm = combination 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 whats the best evidenced?
## Augmentation Strategies for Refractory Depression

<table>
<thead>
<tr>
<th>Evidence-Level</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Lithium</td>
</tr>
<tr>
<td>A/B/C</td>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td></td>
<td>Aripiprazole, Quetiapine</td>
</tr>
<tr>
<td>B</td>
<td>Triiodothyronine (T3)</td>
</tr>
<tr>
<td>C</td>
<td>L-Thyroxine</td>
</tr>
<tr>
<td></td>
<td>Buspirone</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td></td>
<td>Estrogen</td>
</tr>
<tr>
<td></td>
<td>Dopaminagonists</td>
</tr>
<tr>
<td></td>
<td>Psychostimulants</td>
</tr>
</tbody>
</table>

Meta-analysis: Placebo-controlled lithium augmentation studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Lithium n/N</th>
<th>Control n/N</th>
<th>Fixed-effects OR (95% CI)</th>
<th>Fixed-effects OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heninger et al (1983)</td>
<td>5/8</td>
<td>0/7</td>
<td>23.57 (1.00, 556.08)</td>
<td></td>
</tr>
<tr>
<td>Kantor et al (1986)</td>
<td>1/4</td>
<td>0/3</td>
<td>3.00 (0.09, 102.05)</td>
<td></td>
</tr>
<tr>
<td>Zusky et al (1988)</td>
<td>3/8</td>
<td>2/8</td>
<td>1.80 (0.21, 15.4)</td>
<td></td>
</tr>
<tr>
<td>Schöpf et al (1989)</td>
<td>7/14</td>
<td>0/13</td>
<td>27.00 (1.35, 541.57)</td>
<td></td>
</tr>
<tr>
<td>Browne et al (1990)</td>
<td>3/7</td>
<td>2/10</td>
<td>3.00 (0.35, 25.87)</td>
<td></td>
</tr>
<tr>
<td>Stein &amp; Bernadt (1993)</td>
<td>2/16</td>
<td>4/18</td>
<td>0.50 (0.08, 3.19)</td>
<td></td>
</tr>
<tr>
<td>Joffe et al (1993)</td>
<td>9/17</td>
<td>3/16</td>
<td>4.88 (1.01, 23.57)</td>
<td></td>
</tr>
<tr>
<td>Katona et al (1995)</td>
<td>15/29</td>
<td>8/32</td>
<td>3.21 (1.09, 9.48)</td>
<td></td>
</tr>
<tr>
<td>Baumann et al (1996)</td>
<td>6/10</td>
<td>2/14</td>
<td>9.00 (1.27, 63.89)</td>
<td></td>
</tr>
<tr>
<td>Nierenberg et al (2003)</td>
<td>2/18</td>
<td>3/17</td>
<td>0.58 (0.08, 4.01)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53/131</td>
<td>24/138</td>
<td>3.11 (1.80, 5.37)</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=11.90$, df=9, $p=0.22$, $I^2=24.4\%$
Test for overall effect: $Z=4.016$, $p<0.001$

Overall pooled rates of response: lithium, 40.5%; placebo, 17.4%
Meta-analysis of 10 Placebo-RCTs
lithium augmentation vs placebo

Response (%)

<table>
<thead>
<tr>
<th></th>
<th>Lithium</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=269</td>
<td>*p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>NNT=5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*n=269
NNT=5

Why lithium?
Summary of arguments

- Largest database in support of this strategy
- Only add-on treatment with efficacy data in continuation phase
- Long-term experience of > 60 years
- Additional “anti-suicidal” effects
- Preliminary data for pharmacogenetic markers for response prediction

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)

Glycogen synthase Kinase 3 Beta (GSK3β) Genotype and Response to Lithium Augmentation in Major Depression Cox Regression Survival Analysis

-50T/C Single Nucleotide Polymorphism (SNP) in the promotor region of GSK3β gene

Carrier of the C-allels demonstrate significant faster time to remission

N=70

Adli et al. (2007) Biol Psychiatry
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

* 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

MDD Study 6

Week

MDD Study 7

Week

LSM change from baseline in MADRS total score

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

Patients with an inadequate response to AD during current episode

El-Khalili et al. *Int J Neuropsychopharmacol* 2010;13:917
Pooled MDD 6 and 7: MADRS response\textsuperscript{a} and remission\textsuperscript{b} at Week 6

**\textsuperscript{p}<0.01; ***\textsuperscript{p}<0.001 vs placebo**

MITT; LOCF

\textsuperscript{a}≥50\% reduction in MADRS total score from randomisation;

\textsuperscript{b}MADRS total score ≤8

Bauer et al 2010
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\textsuperscript{a}

Quetiapine XR monotherapy\textsuperscript{a}

Add-on lithium to ongoing SSRI / venlafaxine\textsuperscript{b}

Enrolment (Day -14 to -1)
Randomisation

D1 D4 D8

D43

Treatment period (6 weeks)

\textsuperscript{a}Quetiapine XR titration: Day 1-2, 50 mg; Day 3-4, 150 mg; Day 5-43, 300 mg;
\textsuperscript{b}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

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Add-on quetiapine XR (n=229)</th>
<th>Quetiapine XR monotherapy (n=225)</th>
<th>Add-on lithium (n=221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>52.4</td>
<td>50.7</td>
<td>46.2</td>
<td></td>
</tr>
</tbody>
</table>

p = 0.6912

Remission rate

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>MADRS total score ≤8</th>
<th>MADRS total score ≤10</th>
<th>MADRS total score ≤12</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.3</td>
<td>15.6</td>
<td>20.4</td>
<td>31.9</td>
</tr>
<tr>
<td>p = 0.4924</td>
<td>p = 0.9401</td>
<td>p = 0.5474</td>
<td>p = 0.3416</td>
</tr>
</tbody>
</table>

MADRS response defined as a ≥50% reduction in total score from baseline

MITT population
WFSBP recommendation: augmentation strategies

Adding lithium to ongoing antidepressant treatment is recommended in case monotherapy failed.
CE A, RG 2

Lithium augmentation should be administered for 2–4 weeks in order to allow assessment of the patient’s response. The recommended lithium serum target levels are 0.6 to 0.8 mmol/L. In case of response, lithium augmentation should be continued for at least 12 months.2,3
CE A, RG 2

The augmentation of antidepressants with quetiapine or aripiprazole represents an alternative to lithium augmentation and is recommended in case monotherapy failed. Potential unwanted effects include sedation (quetiapine), weight gain (quetiapine, and to a lesser extent aripiprazole) and akathisia (aripiprazole).
CE A, RG 2

WFSBP Treatment Guidelines Major Depressive Disorder, Bauer et al., World Journal of Biological Psychiatry, 2013
Thyroid & Brain Interactions

Imaging and genetic technology

Mood Disorders
Lithium

Thyroid System Hormones
TRH, TSH, T3, T4
Overview: Use of Thyroid Hormone for Treatment of Mood Disorders

ACCELERATION - Speed response
• T3 (25-50 mcg) in unipolar depression (UP)

AUGMENTATION - Convert nonresponder
• T3 (25-50 mcg) in treatment-resistant UP
• Supraphysiological doses of T4 (300-500 mcg) in treatment-resistant depression

MAINTENANCE - Prophylaxis, prevent episodes
• Supraphysiological doses of T4 (300-500 mcg)
• Rapid cycling & refractory bipolar disorder

Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Levothyroxine (L-T₄ - 300 mcg) as Add-on Treatment in Bipolar Depression – Study Design

<table>
<thead>
<tr>
<th>Single-blind Run-in-Phase</th>
<th>Double-blind Study-phase</th>
<th>Open phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Week</td>
<td>6 Weeks</td>
<td>6 Weeks</td>
</tr>
</tbody>
</table>

- Antidepressant and/or Mood-Stabilizer
- Levothyroxine 100 – 200 – 300 µg/d
- Placebo
- Levothyroxine 100 – 200 – 300 µg/d

1st FDG-PET
2nd FDG-PET

The Stanley Medical Research Institute, trial grant # 02T-238 (P.I. M. Bauer)
Change in depression scores (HAMD) during 6-wk of treatment with levothyroxine

ITT – Population, LOCF analysis

Stamm et al. (2013) J Clinical Psychiatry in press
Primary outcome: Change in HRDS-17; ANOVA P = 0.12

* p<0.05
L-thyroxine does not separate from placebo in men, but in women.

Stamm et al. (2013) *J Clinical Psychiatry*, in press
Strategies
When to change strategy?

- Many placebo-controlled trials do not show a significant effect of treatment before Week 3
- Traditional belief is that antidepressant response usually appears with a delay of several weeks
- 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$_{17}$
- 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
Predictive value of early improvement and early non-improvement

- Early improvement in symptoms (20% QIDS-C improvement at Week 2) is highly predictive of treatment response at Week 6
- Negative and positive predictive values approximately 70%
- CGI-I also showed high predictive value
- Consistent with findings of a meta-analysis of 11 studies

CGI-I, Clinical Global Impression-Improvement
QIDS-C, 16-item Quick Inventory of Depressive Symptomatology-Clinician rating score
Gorwood et al 2013
Predictive value of early improvement and early non-improvement

Patients included: n=2938

ITT population: n=2726

Analysis population: n=2351

Non-responders: n=488 (30.3%)

Responders: n=1032 (69.7%)

Early improvement: n=1480 (63.0%)

Responders: n=1032 (69.7%)

Non-responders: n=488 (30.3%)

No early improvement: n=871 (37.0%)

Responders: n=264 (30.3%)

Non-responders: n=607 (69.7%)

Gorwood et al 2013
Early switch strategy versus conventional switch strategy

Time to confirmed remission

Survival distribution function estimate

Early switch strategy (n=282)
Conventional switch strategy (n=284)

Patients with MDD and <30% reduction in HAM-D17 score at Week 4
Early switch strategy: switch to duloxetine for 12 weeks
Conventional switch strategy: 4 further weeks on escitalopram, then switch to duloxetine for non-response or continue on escitalopram in case of response

6.0 vs 7.9 weeks (25% KM estimate); p=0.075

Romera et al 2012
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
Algorithmic strategies
Strategies for the treatment of nonpsychotic MDD
(Texas Medication Algorithm Project)

Stage 1
Monotherapy
SSRI, BUP$_{SR}$, NEF, VLFXR or MRT
Any stage(s) can be skipped depending on the clinical picture
Partial response or nonresponse
Response
Stage 1A
Augmentation
Partial response or nonresponse
Continuation

Stage 2
Monotherapy
SSRI, BUP$_{SR}$, NEF, TCA, VLFXR or MRT
Partial response or nonresponse
Response
Partial response
Stage 2A
Augmentation
Partial response or nonresponse
Continuation

Stage 3
Monotherapy
SSRI, BUP$_{SR}$, NEF, TCA, VLFXR, MRT, MAOI
From a class other than used in stage 1 or 2
Partial response or nonresponse
Response
Partial response
Stage 3A
Augmentation
Partial response or nonresponse
Continuation

Stage 4
Lithium augmentation
Partial response or nonresponse
Response
Stage 4
Continuation

Stage 5
Combination antidepressants:
- TCA+SSRI
- NEF+SSRI
- BUP$_{SR}$+SSRI
- BUP$_{SR}$+NEF
Partial response or nonresponse
Response
Stage 5
Continuation

Stage 6
ECT
Partial response or nonresponse
Response
Stage 6
Continuation

Stage 7
Other eg lamotrigine, fluvoxamine,
MRT + BUP, olanzapine, etc. (provide rationale)
Partial response or nonresponse
Stage 7
Maintenance phase when indicated

BUP$_{SR}$, bupropion sustained release; ECT, electroconvulsive therapy; fluox, fluoxetine
MRT, mirtazapine; NEF, nefazodone; SSRI, selective serotonin reuptake inhibitor
TCA, tricyclic antidepressants; VLFXR, venlafaxine extended release

Trivedi et al 2004
Adjusted mean symptoms for all patients according to the IDS-C$_{30}$ during 12-month ALGO compared with TAU (N=350)

IDS-C$_{30}$ total score

Quarter

Baseline 1 2 3 4

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

IDS-C$_{30}$, 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
- Further diagnostic evaluation
- Exclude organic disorders
- 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
- Switch to next step

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

Proceed to next step
- If remission is not achieved

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
Many patients with MDD do not achieve a satisfactory outcome with antidepressants.

Treatment guidelines recommend dose escalation, switching, combination and augmentation strategies following an inadequate response to antidepressants.

Adjunct therapy with lithium and some atypical antipsychotics is a useful option for patients with inadequate response to antidepressants alone.

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.