Efficacy and feasibility of a treatment algorithm in depressed inpatients

dr. Tom Birkenhager
Dept. of Affective disorders
Erasmus MC Rotterdam
E-mail: t.birkenhager@erasmusmc.nl

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1. What is the use of an algorithm?
2. the Rotterdam study
3. the Berlin study
4. STAR*D study
5. Conclusion

What is the use of an algorithm?

Attaining remission is important

Naturalistic studies (VS): remission is attained by 30% of depressed patients
What is the use of an algorithm?

Inadequately performed pharmacotherapy + 
Unstructured treatment plan

➤ Worse outcome

➤ Chronic course of depression

Treatment-resistant depression

Many different definitions

➤ Absolute resistance

➤ Relative resistance (one adequate treatment)

Many patients labeled “absolute resistant” actually do not fit this category
An algorithm consists of:

a) **strategy**: which treatments are administered?

b) **tactic**: How are these treatments implementated?

c) **treatment steps**: in which order treatments are given

d) critical decision points (evaluation)

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**a. Strategy: what is the basis of the algorithm?**

Assessment of the evidence for specific treatments:

- Literature review and consensus
- Guidelines

How to cope with “lack of evidence”?
b. Implementation

Participating psychiatrists must be willing to make treatment adjustments

Supervision and instruction of treating psychiatrists

Estimation of the feasibility of treatments within a specific setting

Psycho education of patients

c. Different treatment steps in non-responders after 4 weeks

1. Continuation of treatment from 4 to 6-10 weeks
   - With increase of dose

2. Switch to other antidepressant
   - Within same class/other class

3. Augmentation
   - Lithium
   - Mianserine/mirtazapine
   - T3

4. Irreversible, non-selective MAO-inhibitor

5. Electroconvulsive therapy

Multidisciplinary Guideline Depression, 2005
d. Critical Decision Points (CDPs)

- Predefined timepoints
- Marking the moment of evaluation
- Assessment of efficacy with a rating scale (HAM-D)
- Applying response criteria (e.g. 50% improvement)

2. Rotterdam study: inclusion

- Depressed inpatients
- Depressive disorder DSM IV (SADS)
- 17-HAM-D ≥17
- 18-65 years
Rotterdam study:
Overall result of four subsequent steps

Reasons for exclusion

Antidepressant refractoriness : 56 patients
Bipolar depression: 34 "
Acute ECT indication: 18 "
Somatic illness: 11 "
Language barrier: 5 "
Over 65 years 44 "

Total 168

Eligible patients n=342
Randomized n=149
Imipramine (n=70)
  Drop out (n=5)
  Worsening (n=2)
  Side effects (n=3)
  Analyzed n=70
Fluvoxamine (n=68)
  Drop out (n=2)
  Side effects (n=1)
  Discharge (n=1)
  Analyzed n=68

Excluded (n=159)
Refused (n=33)
Placebo response (n=1)
Patient characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age (mean SD)</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>9.5</td>
</tr>
<tr>
<td>male/female</td>
<td>48/101</td>
</tr>
<tr>
<td>Index episode &gt; 1 year</td>
<td>61 (41%)</td>
</tr>
<tr>
<td>First episode</td>
<td>76 (51%)</td>
</tr>
<tr>
<td>Psychotic features</td>
<td>52 (35%)</td>
</tr>
<tr>
<td>Adequate previous treatment with antidepressants</td>
<td>65 (44%)</td>
</tr>
<tr>
<td>Baseline HAM-D</td>
<td>24.6</td>
</tr>
<tr>
<td></td>
<td>5.1</td>
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</table>

Study design Step 1 and 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>3 days</th>
<th>4 days</th>
<th>variable</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>drug-free</td>
<td>placebo</td>
<td>study-medicatin</td>
<td>dose adjustment</td>
</tr>
<tr>
<td>↑ admission</td>
<td>↑ baseline assessment</td>
<td>↑ HRSD &gt; 18</td>
<td>↑ HRSD outcome</td>
<td></td>
</tr>
</tbody>
</table>
Rotterdam study:
Overall result of five subsequent steps

Method

Inpatients
Major depressive episode (n=149)

<table>
<thead>
<tr>
<th>Step</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NA: wash out</td>
<td>≥7 days</td>
</tr>
<tr>
<td>2</td>
<td>AD: fluvoxamine or imipramine</td>
<td>6 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Lithium addition</td>
<td>5 weeks</td>
</tr>
<tr>
<td>4</td>
<td>MAO-I: tranylcypromine or phenelzine</td>
<td>5 weeks</td>
</tr>
<tr>
<td>5</td>
<td>ECT</td>
<td>flexible</td>
</tr>
</tbody>
</table>

Max: 17 wk+ 2 wk washout+ECT

Birkenhäger et al, J Clin Psychiatry 2006

Algorithm

TCA → Response

Nonresponse → Lithium addition → Response

Nonresponse → MAOi → Response

Nonresponse → ECT → Response → Continuation Rx
Step 2: antidepressant monotherapy (6 weeks)

Imipramine with plasmalevel 200-300 ng/ml during 4 weeks (mean dose: 253 mg)

OR

Fluvoxamine with plasmalevel 150-200 ng/ml during 4 weeks (mean dose: 287 mg)

Number of patients attaining a therapeutic plasma level (imipramine)
Step 3: Lithium addition (5 weeks)

Continuation of antidepressant

lithium was added with lithium level 0.6-1.0 mmol/l during 3 weeks

Mean lithium level: 0.80 mmol/l

Step 4: MAOIs (5 weeks)

Tranylcypromine OR Phenelzine initial dose 2x 10 mg,

Twice weekly dose increment

Max dose: 100 mg daily

Mean dose: Tranylcypromine 60.5 mg
Phenelzine 79 mg
Not effective when melancholic features are absent

**Electroconvulsive therapy**

- Bitemporal electrode placement
- Frequency: 2x per week
- Without concurrent psychotropics
- ECT is continued until remission or plateau
<table>
<thead>
<tr>
<th>Stap</th>
<th>Totaal</th>
<th>Respons N (%)</th>
<th>Remissie N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washout</td>
<td>149</td>
<td>11 (7)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Antidepressivum</td>
<td>138</td>
<td>57 (41)</td>
<td>32 (23)</td>
</tr>
<tr>
<td>Lithium additie</td>
<td>71</td>
<td>42 (59)</td>
<td>42 (59)</td>
</tr>
<tr>
<td>MAOI</td>
<td>22</td>
<td>10 (45)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>ECT</td>
<td>11</td>
<td>9 (82)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Overall</td>
<td>149</td>
<td>129 (87)</td>
<td>89 (60)</td>
</tr>
</tbody>
</table>

Dropout: 15%
Conclusions

50% of admitted patients participated

Low dropout rate (15%)

Favourable outcome: 87% response
   60% remission

- Lithium addition and ECT particularly effective

Why was the algorithm effective?

Specialized character depression units

Exclusion of proven refractory depressed patients

Refraining from concurrent psychotropics (benzodiazepines, antipsychotics)

Adherence to the algorithm
3. Berlin study

A randomized open comparison between a Standardized Treatment Regimen (algorithm) and Treatment as usual (TAU)

3. Berlin study: Standardized Stepwise Drug Treatment Regimen (SSTR) versus Standard Treatment as Usual (STU)

<table>
<thead>
<tr>
<th>Step</th>
<th>SSRT Treatment steps</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Withdrawal of previous medication</td>
<td>≤ 3 days</td>
</tr>
<tr>
<td>2</td>
<td>Sleep deprivation</td>
<td>4-7 days</td>
</tr>
<tr>
<td>3</td>
<td>Antidepressant monotherapy</td>
<td>2 wk</td>
</tr>
<tr>
<td>4</td>
<td>High-dose antidepressant monotherapy</td>
<td>2 wk</td>
</tr>
<tr>
<td>5</td>
<td>Lithium augmentation</td>
<td>4 wk</td>
</tr>
<tr>
<td>6</td>
<td>Lithium mono</td>
<td>2 wk</td>
</tr>
<tr>
<td>7</td>
<td>MAO inhibitor - lithium combination</td>
<td>2 wk</td>
</tr>
<tr>
<td>8</td>
<td>High-dose MAO-I - lithium combination</td>
<td>2 wk</td>
</tr>
<tr>
<td>9</td>
<td>Discontinuation</td>
<td>1 wk</td>
</tr>
<tr>
<td>10</td>
<td>ECT (3 per week)</td>
<td>4 wk</td>
</tr>
</tbody>
</table>

Bauer et al, JCPP 2009
Berlin study: comments

A choice for many steps: 10 steps in 21 weeks!

Flaws:

tapering of medication in 3 days
Antidepressant monotherapy 4 weeks
Lithium monotherapy: rationale?
MAO-I (+ li): 4 weeks
ECT: 3x/week, max 12x

Berlin study: comments cont’

Antidepressants: amitriptyline 150 mg
venlafaxine 225 mg
paroxetine 40 mg

High-dose AD: amitriptyline 300 mg
venlafaxine 375 mg
paroxetine 80 mg

Concurrent medication: haloperidol max 10 mg!
Berlin study: comments cont’

MAOi: Tranylcypromine 20 mg  wk 0-2
Tranylcypromine 40 mg  wk 2-4

Standardized Stepwise Drug Treatment Regimen (SSTR) versus Standard Treatment as Usual (STU)

Results
N = 148
ICD 10: depressive episode

SSTR
n = 74 (100%)
- dropouts  n = 33 (44,6%)
- completer  n = 41 (55,4%)
  - no remission  n = 1 (1,4%)
  - full remission  n = 40 (54,1%)

STU
n = 74 (100%)
- completer  n = 62 (83,8%)
- dropouts  n = 12 (16,2%)
  - no remission  n = 33 (44,6%)
  - full remission  n = 29 (39,2%)

Difference: 14.9% (p = 0.07)
Standardized Stepwise Drug Treatment Regimen (SSTR) versus Standard Treatment as Usual (STU)

Survival analysis (itt)

Bauer et al, J Clin Psychopharmacol, 2009

4. STAR*D study

Level 1  SSRI: Citalopram

Level 2  Switch: Sertraline vs. Bupropion vs. Venlafaxine vs. CT
          Or  Addition (to Cit): Buspirone vs. Bupropion vs. CT

Level 3  Switch: Mirtazapine vs. Nortriptyline ↔
          Or  Addition (to Ser, Bup, Ven, Cit): Lithium vs. T3

Level 4  Switch: Tranylcypromine vs. Venlafaxine + Mirtazapine ↔
**STAR*D**

**Level 1**
- Citalopram

**Level 2**
- **Switch options**
  - Ser
  - Bup
  - Ven
  - CT

- **Augmentation options**
  - Cit + Bup
  - Cit + Bus
  - Cit + CT

**Level 3**
- **Switch options**
  - Mirt
  - Nort

- **Augmentation options**
  - Ser + Li/T3
  - Bup + Li/T3
  - Ven + Li/T3
  - Cit + Li/T3

**Level 4**
- **Switch options**
  - TCP
  - Ven + Mirt

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**First step: Citalopram**
- Many patients did not tolerate citalopram (16% severe AE)
- Many patients dropped out < 8 weeks
- Overall low remission and response rates: (28% and 47%)

**Second step: switch or augmentation**
- Also low remission and response rates
  - **Switch**: 18-25% and 25-27%
  - **Augmentation**: 30% and 27-32%
Rationale for different choices
   Why buspirone?
   Why not a TCA or mirtazapine augmentation in level 2?

External validity
   Appears high: many patients, many centers

Internal validity: Some major limitations
   No placebo group
   Not double-blind
   High drop out rate
   Diagnosis doubtful

STAR*D: Level 3 augmentation

   Bupropion
   Sertraline + Lithium addition/
               T3 addition
   Citalopram
   Venlafaxine

Nierenberg et al, Am J Psychiatry 2006
STAR*D: level 3

Lithium addition (n=69)
T3 addition (n=73)

Mean age: 40.6 y
Mean index episode: 29 mo
Mean number of episodes: 8.4
Melancholic features: 16.4%

dysthymia/chronic depression without melancholic or psychotic features

STAR*D: level 3

9.6 weeks lithium addition (max 900 mg):
15.9% remission

9.6 weeks T3 addition (max 50 µg):
24.7% remission
Lithium addition: conclusion

Lithium added to:

- a variety of modern antidepressants
- with unknown/low lithium levels
- in patients dysthymia/chronic depression without melancholic or psychotic features
- is ineffective

STAR*D level 4: Tranylcypromine

- Tranylcypromine (n=58)
- Venlafaxine-mirtazapine (n=51)

- Mean index episode: 43.5 mo
- Mean number episodes: 9.0
- Melancholic features: 24.0%
STAR*D level 4: Tranylcypromine

12 wk; mean dose TRAN 36.9 mg
    mean dose VLF-MRT 210+35 mg

TRAN: 6.9 % Remission
VLF-MRT: 13.7% Remission

Tranylcypromine: conclusion

(very) low doses of tranylcypromine
in patients with dysthymia/chronic depression
are ineffective
General conclusion

Algorithms for the treatment of major depression can be effective

But: some interventions (Lithium addition, ECT) are effective in melancholic depression

In depression without melancholia/ dysthymia these treatment steps may be ineffective (ECT, maybe also lithium addition)

General conclusion

The treatment algorithm should be appropriate for the type of major depression

One size fits none!
Thank you for your attention