Management of Refractory Depression

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Contents

• Diagnosis
  – Defining depression
  – Clinical classification

• Management
  – Refractory depression
    • Treatment resistant depression
    • Response v remission
  – Management by sub-type
    • Non-melancholic depression
    • Melancholic Depression
      – Unipolar v bipolar
      – Psychotic depression
Diagnosis
Essence of major depression

High prevalence *group* of disorders characterized by

- morbid and pervasively negative mood
- depressive cognitions
- neuro-vegetative disturbance
- variable degrees of psychomotor change
Course of major depression

Typically follow a chronic fluctuating or recurrent episodic course

- High morbidity
- Significant mortality
- Often associated with psychiatric co-morbidity
- Often associated with medical co-morbidity
The Classificatory Debate

• “lack of a highly reliable or valid classificatory system has significant and practical clinical consequences, particularly in primary care where the full range of depression presents”

• “concern is whether depression should be classified using dimensions or categories”

• clinicians required to make a categorical decisions – antidepressants or not, specialist referral or not
Essence of major depression

♦ Depressed mood - morbid and pervasive

♦ Depressive cognitions
  – hopelessness (-ve future)
  – helplessness (-ve environment)
  – worthlessness, guilt (-ve self)

♦ Neurovegetative disturbance
  – sleep, DMV, anhedonia
  – appetite, wt
  – energy, concentration, libido

♦ Psychomotor changes - agitation/retardationy

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Dimensional v Categorical Classification

• Categorical model (hierarchical model which is clinically useful)
  – a group of disorders (incorporates bipolarity)
    • non-melancholic depression (‘reactive’)
      – with anxiety (internalising)
      – with hostility (externalising)
    • melancholic depression (‘endogenous’)
      – unipolar v bipolar disorders
      – atypical depression
      – psychotic/agitated depression (melancholia + psychosis)
Dimensional v Categorical Classification

• Dimensional model (DSM IV & ICD 10)
  – A single disorder (bipolarity separate)
    • major depressive disorder – single episode v recurrent
      – Severity mild moderate severe
    • DSM 5 specifiers includes mixed features
      – anxious distress
      – melancholic features
      – atypical features*
      – mood-congruent psychotic features
      – mood-incongruent psychotic features*
      – catatonia*
      – mixed features*
      – peripartum onset*
      – seasonal pattern
DSM V – Grief v Depression

• Responses to a significant loss - bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability - may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss which may resemble a depressive episode

• A major depressive episode may occur in addition to the response to a significant loss

• Decision requires the exercise of clinical judgment based on history and cultural norms for the expression of distress
Depression-like states

• Sub-syndromal depressive symptoms
  – Acute
    • Grief/Adjustment disorder
    • Substance induced mental disorder
    • Sub-syndromal episode of primary mood disorder
  – Chronic
    • Persistent depressive disorder (replaced dysthymia & incorporated chronic residual symptoms of MDD)
    • Cyclothymia (disorder or sub-syndromal bipolarity?)
    • Substance induced mental disorder
Clinical sub-typing of depression

• Major Depression
  – Melancholic
    • unipolar v bipolar
    • ? with psychotic or agitated features
    • atypical
  – Non-melancholic
    • with anxiety (internalising)
    • with hostility (externalising)
Recurrence Becomes More Likely With Each Episode of Depression

Recurrence risk (%) following recovery during long-term follow-up*

First episode¹-³  >50%
Second episode²  ≈70%
Third + episode²  ≈85%

*Patients were followed for 3 to 15 years following recovery from previous episode.

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Stressful Life Events as a “Trigger” for Depression Progressively Declines

No. of previous depressive episodes

Risk (%) of depression onset per month

“Kindling” Phenomenon

With increasing depressive episodes:

↑ Risk of depression
↓ Association with stressful life events

Response v Remission

- 1/3 of patients fail to achieve an adequate response to therapy\(^1,2\)
- Health, social & economic burden of refractory depression
  - ↑ risk of relapse
  - ↑ morbidity & mortality
  - ↑ health care costs
  - ↑ carer burden
  - ↓ social functioning
  - ↓ productivity
- Remission optimal but not always feasible
Refractory Depression

- usually 3 AD trials are needed before the majority of patients respond to the point of remission \(^1\)
- patients aim for recovery .... doctors aim for remission\(^2\)
Def’n of Refractory Depression (TRD)

- No agreed definition of treatment resistance

- **Minimum**
  - depression that does not fully remit with initial treatment

- **Standard**
  - “major depression (not 20 to substance or medical condition) that has failed to respond, or to sustain response to an adequate trial of standard antidepressant”\(^1\)

- **Maximum**
  - Failure to respond to at least two antidepressants from different classes in conjunction with at least one recognised psychotherapy
Residual Symptoms and Number of Episodes May Influence the Course of Illness

Weeks to First Prospective Relapse to any Depressive Episode

<table>
<thead>
<tr>
<th>Recovery</th>
<th>Previous episodes</th>
<th>N</th>
<th>Median weeks well</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>1–3</td>
<td>121</td>
<td>224.0</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>3+</td>
<td>34</td>
<td>79.0</td>
</tr>
<tr>
<td>Residual SSD</td>
<td>1–3</td>
<td>57</td>
<td>34.0</td>
</tr>
<tr>
<td>Residual SSD</td>
<td>3+</td>
<td>25</td>
<td>28.0</td>
</tr>
</tbody>
</table>

MDD=Major depressive disorder; SSD=Subsyndromal symptoms of depression; Survival distribution function=Cumulative proportion of cases surviving to given time interval.

Relapse if remission is not achieved?

% of Patients Who Relapsed (2-year Follow-up Study)

<table>
<thead>
<tr>
<th>Patients in Partial Remission</th>
<th>Patients in Complete Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>67.6%</td>
<td>15.2%</td>
</tr>
</tbody>
</table>

*p<0.0001

Longer term treatment outcomes: value of effective Rx

• Rapid remission most important predictor long-term (N=196, 2-year study)\(^1\)
• Longer previous episode reduced the likelihood of recovery by 37% (N=250, 2-year study)\(^2\)
• Lower relapse rates if in remission at follow-up (N = 2238 STAR*D with 12 month follow up)\(^3\)
• Lack of response to first antidepressant predicts future treatment resistance (N=702)\(^4\)

Partial response increases relapse

Figure 8. Residual depressive symptoms are associated with greater risk of relapse.

Among patients with residual symptoms, > 90% had mild to moderate general somatic symptoms

Risks of refractory depression

• Greater risk of relapse/recurrence\(^1\)-\(^3\)
• More chronic depressive episodes\(^1\)
• Shorter durations between episodes\(^1\)
• Continued impairment in work and relationships\(^4\)
• Increase in all-cause mortality\(^5\) and morbidity and/or mortality with stroke,\(^6\) diabetes,\(^7,8\) MI,\(^9\) CVD,\(^10\) CHF,\(^11\) HIV,\(^12\) etc
• Sustained risk of suicide\(^13\)
• Long term remission difficult to achieve and maintain\(^14\)
  • 80% with remission from multiple treatments \(\Rightarrow\) relapse < 1 year
  • Protracted illness only 40% recovery over 10 years

Depression & Neuro-anatomic Changes

- Evidence of correlation between neuro-anatomic changes and disease is rapidly expanding\(^1\)-\(^7\):
  - Hippocampal volume reduced in major depression
  - Changes greater with chronic or recurrent disease
  - Volume changes may persist after resolution
  - Changes either precede illness onset or originate with chronic illness

Areas of increased activation in patients with MDD at rest and decreased activation compared with controls.

**Increased activity**: LOPFC, VMPFC, amygdala, thalamus, caudate nucleus.

**Decreased activity**: DLPFC, insula, pregenual and dACC, superior temporal gyrus.

dACC=Dorsal anterior cingulate cortex; DLPFC=Dorsolateral prefrontal cortex; LOPFC=Lateral orbital prefrontal cortex; MDD=Major depressive disorder; VMPFC=Ventromedial prefrontal cortex.

Summary: Structural and Functional Changes in MDD

MDD = Major depressive disorder.

Can Treatment Prevent or Reverse the Damage?

STRESS

↑ Glucocorticoids
↓ BDNF

Normal survival and growth

↓ Dendritic branching of neurons
↓ Atrophy/death of neurons

??

Increased survival and growth

↑ BDNF
↓ Glucocorticoids
↑ 5-HT and NE

Pharmacotherapy, ECT, psychotherapy, rTMS, exercise

Sapolsky RM. Arch Gen Psychiatry. 2000;57:925-935.

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Management
Do antidepressants work?

Kirsch et al 2008 Plos Initial Severity and Antidepressant Benefits: A Meta-Analyses of Data Submitted to the Food and Drug Administration
Cognitive Therapy and Medications Affect the Brain in Complementary Ways

ADM=Antidepressant medication; CT=Cognitive therapy; PFC=Prefrontal cortex.


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Depression: overall treatment strategies

• Remove or control contributing factors
• Psycho-education re depression
• Phase specific psychotherapy
• Stress management/exercise
• Targeted dosing of primary medication
  – Antidepressants if unipolar
  – Mood stabilisers if bipolar
  – Specialist care/combinations if high acuity
Treatment Strategies 2

• Psychosocial
  – Psychotherapy
    • Supportive & Structured problem solving
    • Interpersonal & Cognitive-behavioural therapy
  – Relaxation training
  – Structured time
    • some social stimulation
    • exercise

• Antidepressants
  – SSRI’s
  – SNRI/NaSSA
  – TCA’s & heterocyclic AD
  – RIMA’s, MAOI’s
Treatment Strategies 3

- Other Pharmacotherapy
  - Acute phase/severe anxiety
    - add benzodiazepines
  - Psychotic depression/severe melancholic depression
    - add antipsychotics
  - Bipolar depression - additional
    - atypical antipsychotics
    - lamotrigine

- ECT
  - Rx of choice in psychotic depression or severe melancholic depression
Factors to Consider in Patients Failing First Trial of Antidepressant Monotherapy

- Correct Diagnosis
- Comorbid psychiatric conditions
- Appropriate drug therapy
- Severity of illness
- Compliance
- Adequate dose
- Adequate duration
- Comorbid medical conditions
- Treatment refractory patient
Whats next?

Switch
- If no/partial response
- Preferably a different class
- TCA or SNRI for melancholia
- SSRI or AGM or NaSSA or MAOI if bipolar & mood stabilised

Augment/Combine
- If partial response
- Choose augmentation based on subtype of depression or comorbidity
  - Psychotherapy
  - AAP
  - Lithium
  - 2nd AD

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Augmentation Strategies

Primary AD

- Exercise
- CBT, IPT & mindfulness psychotherapy
- Atypical Antipsychotic
- Mood Stabilizer
- Lithium/T3
- Other e.g. Stimulants
- ECT & other brain stimulation
- 2nd AD

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ECT for Depression
rTMS for Depression

NeuroStar stimulates neurons in the prefrontal cortex to restore normal function in these local areas.

1. NeuroStar stimulates neurons in the prefrontal cortex to restore normal function in these local areas.

2. Neurons in the prefrontal cortex communicate to deeper brain neurons.

3. Stimulation of deeper brain neurons causes a secondary effect on remaining portions of the brain involved in mood.

Left Prefrontal Cortex

Anterior Cingulate Cortex

Amygdala

Hippocampus
tDCS for Depression

- Brunoni et al.
- SELECT / ELECT
- target: DPLPC
- 2.0 mA
- Double blind RCT

- Loo et al.
- Multi-Center Trial
- target: DPLPC
- 2.5 mA
- Double blind RCT

Reality

DIY tDCS
Keeping Tabs On Transcranial Direct Current Stimulation
DBS for depression
Refractory depression

• Most refractory depression is due to either
  – inadequate biological treatment of melancholic depression

  or

  – inadequate psychosocial treatment of non-melancholic depression
Melancholic Depression - Unipolar

- Psycho-education re depression as treatable brain illness
- Optimise pharmacotherapy
  - Broad spectrum AD
    - SNRI, TCA (therapeutic serum monitoring), MAOI
  - Augment
    - Atypical antipsychotics – e.g. olanzapine 2.5-10mg
    - Lithium
    - Stimulant
    - ? T₃
  - Combination AD
    - SNRI + NaSSA/AGM/Buproprion
    - SSRI + NaSSA/AGM/Buproprion
    - Specialised combinations TCA + SSRI, TCA + MAOI

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Melancholic Depression - Bipolar

- Optimise pharmacotherapy starting with mood stabiliser
  - Lithium
  - Augment
    - Atypical antipsychotic – e.g. OLZ or QTP
    - Lamotrigine
  - Care with AD
    - SSRI
    - MAOI
  - ECT highly effective v medication
- Other
  - Stimulant
  - ? T₃
Melancholic Depression

• **Electro-Convulsive Therapy (ECT)**\(^1\)\(^-\)\(^5\)
  - Rapid and increased rates of both response and remission
  - Modern approaches less acute confusion/memory disturbance
  - Older patients response rates >> than to medication
  - Bipolar patients response rates >> than to medication
  - **Response**
    - psychotic depression \(\approx 90\%-94\%\) (2/3 remit)
    - melancholia without psychosis \(\approx 80\%\) (2/3 remit)
    - drops to \(\approx 50\%-60\%\) if last line (chronicity \(\downarrow\) likelihood of remission)
  - **Maintenance ECT**
    - Equivalent or better outcomes than pharmacotherapy alone
Melancholic depression with psychosis/agitation

- High risk state psychiatric admission warranted
- Electro-Convulsive Therapy (ECT)
  - equal 1st line as rapid, near certain response
- Combination broad spectrum AD and AAP
  - SNRI (generous dose) or TCA (therapeutic levels) or MAOI
  - Atypical antipsychotics – e.g. olanzapine 2.5-10mg or risperidone 1-4 mg

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Non-melancholic

• Remove / control contributing factors
  – stress management and conflict resolution
• Psycho-educate
  – bio-psycho-social approach to a treatable illness
  – risk/vulnerability and relapse prevention
  – family/partner/carer education - a co-therapist
• Psychotherapy\(^1,2\)
  – Several shown to work (tailor to specific needs) from IPT, CBT, DBT, family or marital therapy
• Exercise/Lifestyle
  – mild to moderate depression
  – best evidence for resistance and HITS

2. Trivedi R et al, J Gen Intern Med 2011
Non-melancholic depression

• Pharmacotherapy
  – Tolerable modern AD aiming for target dose
    • SSRI/NaSSA/AGM/SNRI/Vor
  – Strategies if anxiety/distress ++ severe ++ disabling ++
    • high dose AD /broad spectrum SNRI
    • augmentation lithium or atypical antipsychotics
    • combination AD
    • rTMS or ECT - non-melancholic approx 50-60% still respond

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Non-melancholic depression

• Treat co-morbidity
  – Anxiety
    • Relaxation training/CBT/benzodiazepines
    • OCD Rx
  – ADHD
    • Stimulant/ATX
    • Psychology/Coaching
  – Substance use disorders
    • Treatment programs
    • SUD medications
  – Chronic pain
    • Stabilise analgesia/pregabalin (neuralgic)
    • Rehabilitation model
    • SNRI or TCA
Summary

• Depression typically a chronic relapsing disorder
• Phased multimodal management based on diagnostic sub-type and illness severity
  • Non-melancholic depression
    – multiple treatment options
    – psychological work helpful
    – medication helpful but not essential
  • Melancholic depression
    – active medical management essential
    – psychological work phase dependent
Summary

• Goal usually remission as untreated depression has severe consequences
• Rational poly-pharmacy is good medicine for severely depressed / complex cases
• Brain stimulation options emerging, for now ECT
  – of profound acute benefit for melancholic patients
  – remains an option for intractable illnesses
Case Scenario 1

- 70 year old Japanese-Australian
  - Chronic depression
    - non-melancholic anxious/worrier
  - Chronic abdominal pain
    - opiate dependence in remission
    - pain specialist review – little to offer
  - Alcohol/sedative dependence
    - Partially controlled
  - Serious suicide attempts > 3 occasions
  - SSRI nonresponse, TCA nonresponsive
  - SNRI limited to < 225mg (5HT syndrome)
  - Ltd benefit from CBT/group DBT/fortnightly supportive psychotherapy

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Case scenario 2

• 37 year old Anglo-Australian woman. Mother of two, part time work as nurse.
  – Bipolar disorder type II – severe MDE with melancholia and intense suicidality
  – Violent, controlling and critical father
  – Good marriage, finances OK, no substance use
  – 1st Episode postnatal responded to SSRI and psychotherapy
  – Now depressed failed SSRI at higher doses then TCA – dothiepin and valproate

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