MAJOR DEPRESSIVE DISORDER: NEW DEVELOPMENTS AND PRACTICAL IMPLICATIONS

Jon-Paul Khoo

Objectives

- What is treatment-resistant depression really?
- How can we use this knowledge to improve initial MDD management?
- What are the evidence-based management options when first-line antidepressant treatment fails?

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A practice review

- "What is treatment resistance really?"
- Database review
- 328 consecutive non-remitted MDD patients referred for private outpatient specialist care

A practice review
Why didn't depression get better?

1. Incorrect diagnosis	N (of 328)	%
Alternative Axis I disorder	21	6.4
Secondary (organic) depression	30	9.1
Alternative mood disorder		
Dysthymia	47	14.3
Adjustment disorder	36	11.0
Bipolar disorder	119	36.3
Personality disorder	114	34.8

A practice review
Why didn't depression get better?

2. Specific depressive subtype	N (of 328)	%
Psychotic	41	12.5
Melancholic	135	41.2
Mixed	63	19.2
Anxious	97	29.6
Atypical	89	27.1
Neurotic	58	17.7

A practice review

Why didn't depression get better?

3. Comorbidity	N (of 328)	%
Physical	89	27.1
Psychiatric (Axis I)	207	63.1
Substance	137	41.8
Undiagnosed	165	50.3
Undertreated	57	17.4

A practice review

Why didn't depression get better?

4. Inadequate treatment	N (of 328)	%
Poor adherence	139	42.4
Undertreatment		
Subtherapeutic dose	44	13.4
Inadequate duration	39	11.9

What is treatment resistance really?

Depression that didn't get better

- Depression not remitting (≥ 2 AD trials) 100%
- "Pseudo-resistant depression" 70.4%
  - Incorrect initial diagnosis
  - Specific subtype requiring specific treatment
  - Undiagnosed/undertreated comorbidity
  - Inadequate treatment
- "True" (pharmacological) TRD 29.4%
  - "True" treatment-refractory depression 6.4%

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Better initial management of MDD

- Exclude/address "pseudo-resistance" from the outset
  - (Re)assessing diagnosis including specific subtypes
  - Identifying and treating comorbidity
  - Ensuring adequate initial treatment

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Evidence-based initial treatment

- 2015 RANZCP CPG MDD recommendations
  - Mild to moderate depression
    - Psychoeducation and psychological therapies
  - Moderate to severe depression
    - As above plus antidepressant medication
- Regular monitoring
- Continue antidepressant therapy
  - 1 year after an initial episode
  - 3+ years if recurrent or severe/concerning (psychotic)

Malhi G et al. ANZJP 2015; 49: 1087-1206.

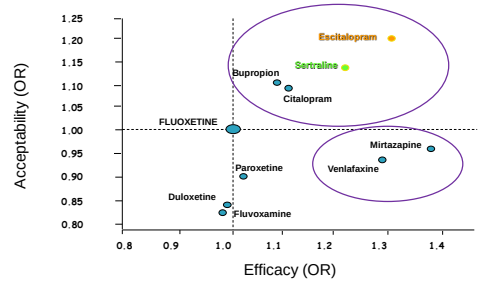
Acute antidepressant treatment
Level 1 evidence

RANZCP 2015	CANMAT 2016*
1. SSRI; NDRI; NaSSA; NRI; agomelatine	1. SSRI; SNRI; NDRI; SM; NaSSA; agomelatine
2. SNRI; TCA; SM	2. TCA; RIMA; AAP;
3. MAOI; RIMA	3. MAOI; NRI

* Excluding pharmaceuticals not currently available in Australia

Malhi G et al. ANZJP 2015; 49: 1087-1206.
Kennedy, S et al. Can J Psychiatry 2016;61(9):540-560.

Multiple treatments meta-analysis of efficacy and acceptability

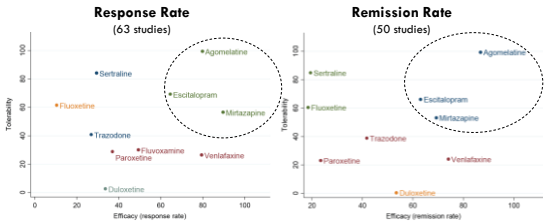


Adapted from: Cipriani A et al. Lancet. 2009 28;373(9665):746-58.

Antidepressant efficacy vs tolerability

16

Meta-analysis of **head-to-head RCTs** of antidepressant monotherapy in the acute treatment of MDD
76 trials from 1989-2014, totaling 16,389 participants



Khoo AL, et al. CNS Drugs. 2015;29:695-712.

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Psychological therapy for MDD

Table 11. Psychotherapy for depression acute phase and maintenance/relapse.

Psychotherapy	Depression acute phase	Depression maintenance/relapse
Cognitive (behavioural) therapy (CBT)	+	+
Interpersonal psychotherapy (IPT)	+	+
Non-directive supportive therapy	+	O
Problem-solving therapy	+	O
Behavioural activation therapy	+	O
Self-control therapy	+	O
Short-term psychodynamic therapy	+	O
Mindfulness-based cognitive therapy (MBCT)	O	+

Note: See Appendix 2 for meta-analytic data on comparative efficacy. 'O' indicates no information available.

Malhi G et al. ANZJP 2015; 49: 1087-1206.

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- What are the evidence-based management options when first-line antidepressant treatment fails?
  - Specific depression-focussed psychological therapy
  - Increase, change or add pharmacotherapy

Pharmacotherapy options for TRD

- Brief discussion of current evidence
  - Increase
  - Change
    - To increase or to change the antidepressant?
    - To change within or between antidepressant class?
  - Add
    - Best adds?
    - To change or to add to the antidepressant?

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- What are the evidence-based management options when first-line antidepressant treatment fails?
  - Specific depression-focussed psychological therapy
  - Increase, change or add pharmacotherapy
    - New therapies currently available

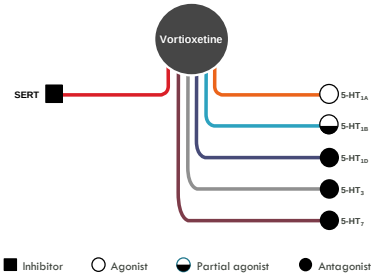
Agomelatine "Valdoxan"

- MT-1 and MT-2 agonist and 5HT-2C antagonist
- Efficacy (Level 1 evidence)
  - Cochrane review 2013
    - As effective as SSRIs and SNRIs
    - Better acceptability than SNRI (VLF)
    - Fewer sexual side effects than SSRIs
  - Some evidence for differentiated efficacy in
    - Clear thinking, emotional range, pleasure

Agomelatine "Valdoxan"

- Tolerability: not evidently associated with:
  - Sexual dysfunction
  - Weight gain
  - Discontinuation symptoms
- Dosing: 25-50mg nocte
  - Contraindications
    - Transaminases >3xULN
    - Potent CYP1A2 inhibitors
  - LFT monitoring: baseline and 3,6,12 and 24 weeks

Vortioxetine "Brintellix"



Serotonin modulator: increases monoamine (5HT, NA, DA) release

Vortioxetine "Brintellix"

- Efficacy (Level 1 evidence)
  - MDD, severe MDD, the elderly and maintenance
  - Comparator studies: agomelatine, duloxetine, venlafaxine
  - Evidence for differentiated efficacy in cognition
- Tolerability
  - Not evidently associated with weight gain or discontinuation
  - Reduced rates of sexual dysfunction
  - Nausea is most common side-effect
- Dosing: 5-20mg OD
  - Primarily metabolised by CYP2D6
    - CYP2D6 inhibitors increase vortioxetine concentration
    - CYP2D6 inducers decrease vortioxetine concentration

Ketamine

- Ionotropic NMDA receptor antagonist
- Efficacy
  - Level 1 evidence, but considered an experimental treatment
  - 50-70% response rates in TRD
  - 2/24 - 2/52 (rapid improvement)
- Utility limited by
  - Transient effects, abuse liability, psychotomimetic effects, IV route and need for administration in a clinical setting
- Dosing
  - 0.5mg/kg (0.1mg/kg) over 40/60 IV infusion (oral? intranasal?)
  - Past history of psychosis may be a relative contraindication

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  - Specific depression-focussed psychological therapy
  - Increase, change or add pharmacotherapy
    - New therapies currently available
  - Neurostimulation

Neurostimulation

- ECT
- rTMS
- tDCS
- MST
- DBS

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Electroconvulsive therapy

- Level 1 evidence (acute and maintenance)
- 70-80% response and 40-50% remission
- Neurocognitive side-effects
- Second line treatment
  - TRD; repeated medication intolerance
- First line treatment if
  - Severe and melancholic; not eating/drinking; high suicide risk; psychotic depression; catatonia; previous response; patient choice

Neurostimulation

- ECT
- rTMS
- tDCS
- MST
- DBS

Repetitive transcranial magnetic stimulation

- Level 1 evidence for acute treatment
- 40-55% response and 25-30% remission
- Greater tolerability and utility than ECT
  - Seizure induction 1:1000-1:10000
- Daily, 5 days/week, 20+ treatments
- First line treatment for patients with non-psychotic MDD failing ≥1 ADT

Neurostimulation

- ECT
- rTMS
- tDCS
- MST
- DBS

Transcranial direct current stimulation

- Level 2 evidence
- Easy, low cost, portable, few side-effects, potential for home use
- Third line treatment recommendation

Neurostimulation

- ECT
- rTMS
- tDCS
- MST
- DBS

Magnetic seizure therapy

- Level 3 evidence: investigational treatment
- Equivalent response/remission to RUL ECT
- Fewer side-effects
  - No apparent neurocognitive difficulties
  - Requires GA, assisted ventilation and EEG monitoring

Neurostimulation

- ECT
- rTMS
- tDCS
- MST
- DBS

Deep brain stimulation

- Implantable neurostimulation technology
- Level 3 evidence: investigational
- Highly refractory patients
  - 30-60% rates and 20-40% remission rates

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- What are the evidence-based management options when first-line antidepressant treatment fails?
  - Specific depression-focussed psychological therapy
  - Increase, change or add pharmacotherapy
    - New therapies currently available
  - Neurostimulation
  - Complimentary and alternative therapies

Complimentary and alternative therapies Summary recommendations

Recommendation	Mild-moderate		Moderate-severe	
	MonoRx	AdjunctRx	MonoRx	AdjunctRx
First line	Exercise			
	St John's Wort			
Second line	O3FA	O3FA	Exercise	
		SAMe		
	Light	Light		St John's Wort
		Yoga		O3FA
				SAMe

Level 1 Evidence Level 2 Evidence

Adapted from Ravondran A, et al. 2016. Can J Psychiatry;61(9):576-587.

Objectives: take home messages

- What is treatment-resistant depression really?
  - "Pseudo-resistance" accounts for the majority of treatment resistance in a real-life referral cohort
- How can we use this knowledge to improve initial MDD management?
  - Address pseudo-resistance from the outset
    - (Re)assessing diagnosis including specific subtypes
    - Identifying and treating comorbidity
    - Ensuring adequate initial treatment
- What are the evidence-based management options when first-line antidepressant treatment fails?
  - Specific depression-focussed psychological treatment
    - Acute: any except MBCT
    - Maintenance: MBCT, CBT, IPT

Take home messages

- What are the evidence-based management options when first-line antidepressant treatment fails? (continued)
  - Increase, change or add pharmacotherapy
    - Increase = change within class = change between class
    - Slight benefit for adding (but not for any specific medication)
      - Best adds: atypical antipsychotics, lithium, T3, (other AD)
    - New agents: agomelatine, vortioxetine and ketamine
  - Neurostimulation
    - ECT, rTMS
  - Consider complimentary and alternative therapies