TREATMENT RESISTANT MDD AND DEPRESSION IN WOMEN

Jon-Paul Khoo

Objectives

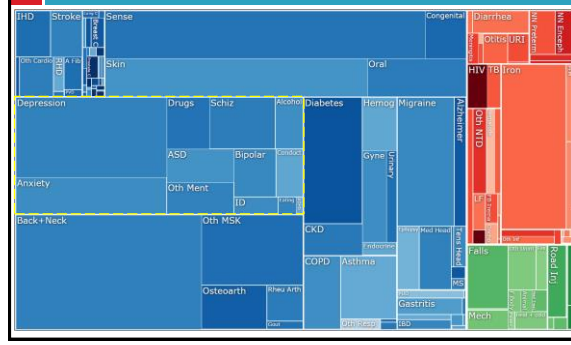
- MDD is a critical public health problem
- MDD in women
- Treatment-resistant depression
  - What is it really
  - Evidence-based management options when first-line antidepressant treatment fails
- Summary

MDD is a critical public health problem

- Common
- Severe and recurrent
- Disabling

Disability (YLDs) GBD 2015

Personal communication, Prof Harvey Whiteford, Professor of Population Mental Health, School of Population Health, Faculty of Medicine and Biomedical Sciences, University of Queensland.



MDD is a critical public health problem

- Common
- Severe and recurrent
- Disabling
- Increased morbidity and mortality
- Costly
- We can do better

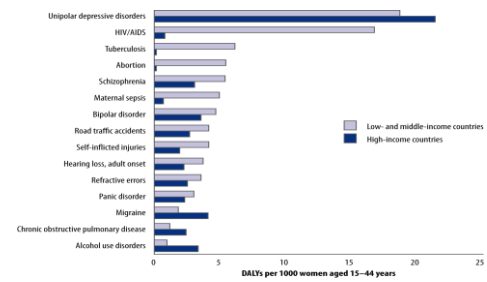
Objectives

- MDD is a critical public health problem
- MDD in women
- Treatment-resistant depression
  - What is it really
  - Evidence-based management options when first-line antidepressant treatment fails
- Summary

MDD in women

- MDD is the leading cause of worldwide disease burden in women

Disease burden for women aged 15–44 years, high and low-and middle-income countries, 2004



Burden of Disease in Australia

Rank	Males	DALYs	% of total	Females	DALYs	% of total
1	Ischaemic Heart disease	151,101	11.0	Anxiety and depression	126,464	10.0
2	Type 2 diabetes	76,577	5.6	Ischaemic heart disease	112,385	8.9
3	Anxiety and depression	65,321	4.8	Stroke	65,173	5.2
4	Lung cancer	55,028	4.0	Dementia	60,734	4.8
5	Stroke	53,302	3.9	Breast cancer	60,518	4.8
6	COPD	49,198	3.6	Type 2 diabetes	55,739	4.4
7	Adult-onset hearing loss	42,646	3.1	COPD	37,548	3.0
8	Suicide and self-harm	38,717	2.8	Lung cancer	33,876	2.7
9	Prostate cancer	36,544	2.7	Asthma	33,828	2.7
10	Colorectal cancer	34,642	2.5	Colorectal cancer	28,961	2.3

Personal communication, Prof Harvey Whiteford, Professor of Population Mental Health, School of Population Health, Faculty of Medicine and Biomedical Sciences, University of Queensland.

MDD in women

- MDD is a leading cause of worldwide disease burden in women
- Unmet need
- The gender gap
- MDD in women is prototypical MDD
- MDD presentations in women

MDD presentations in women

- Depressive phenotypes more common in women
  - Atypical depression
  - Anxious depression
  - Somatic depression
- MDD in the peripartum
- MDD in the peri- and post-menopause
- Proposed gender-related subtypes
  - Developmental subtype
  - Reproductive subtype

Objectives

- MDD is a critical public health problem
- MDD in women
- Treatment-resistant depression
  - What is it really
  - Evidence-based management options when first-line antidepressant treatment fails
- Summary

What is treatment resistance really?

Depression that didn't get better

- Depression that got 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%

How does this inform our initial management?

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

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.

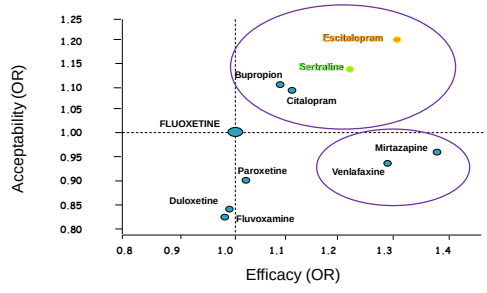
Acute antidepressant treatment
Level 1 evidence

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

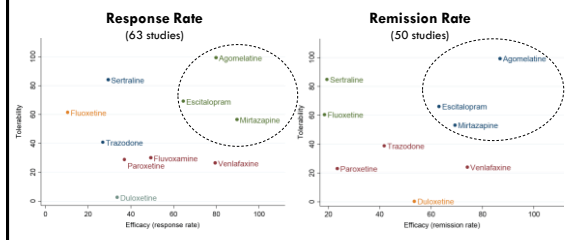


Adapted from: Cipriani A et al. Lancet. 2009 28;373(9665):746-58.

Antidepressant efficacy vs tolerability

18

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.

Objectives

- MDD is a critical public health problem
- MDD in women
- Treatment-resistant depression
  - What is it really
  - Evidence-based management options when first-line antidepressant treatment fails
- Summary

When 1st line antidepressant treatment fails

- Specific depression-focussed psychological therapy
- Increase, change or add pharmacotherapy
- Neurostimulation
- Consider complimentary and alternative therapies
- Referral

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.

When 1st line antidepressant treatment fails

- Specific depression-focussed psychological therapy
- Increase, change or add pharmacotherapy
- Neurostimulation
- Consider complimentary and alternative therapies
- Referral

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?

AD change vs add: a clinical decision

SWITCH ANTIDEPRESSANT

- First AD trial
- Poorly tolerated
- No response
- Time is not critical
- Patient preference

ADJUNCTIVE MEDICATION

- ≥ 2 AD trials
- Well tolerated
- Partial response (>25%)
- Specific targetable residual symptoms
- Less time to wait
- Patient preference

Kennedy, S et al. Can J Psychiatry 2016;61(9): 540-560.

When 1st line antidepressant treatment fails

- Specific depression-focussed psychological therapy
- Increase, change or add pharmacotherapy
- Neurostimulation
- Consider complimentary and alternative therapies
- Referral

Neurostimulation

- ECT — 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
- rTMS

Neurostimulation

- ECT
- rTMS — 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

When 1st line antidepressant treatment fails

- Specific depression-focussed psychological therapy
- Increase, change or add pharmacotherapy
- Neurostimulation
- Consider complimentary and alternative therapies
- Referral

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

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

When 1st line antidepressant treatment fails

- Specific depression-focussed psychological therapy
- Increase, change or add pharmacotherapy
- Neurostimulation
- Consider complimentary and alternative therapies
- Referral

Objectives

- MDD is a critical public health problem
- MDD in women
- Treatment-resistant depression
  - What is it really
  - Evidence-based management options when first-line antidepressant treatment fails
- Summary

Objectives: take home messages

- MDD is a critical public health problem, especially for women
- There are MDD phenotypes more common in women, and particular times in the reproductive cycle where risk may be increased
- "Pseudo-resistance" accounts for the majority of treatment resistance in a real-life referral cohort and should be minimised from the outset
  - (Re)assessing diagnosis including specific subtypes
  - Identifying and treating comorbidity
  - Ensuring adequate initial treatment

Take home messages

- Evidence-based management options when first-line antidepressant treatment fails
  - Specific depression-focussed psychological treatment
    - Acute: any except MBCT
    - Maintenance: MBCT, CBT, IPT
  - Increase, change or add pharmacotherapy
    - Largely a clinical choice (all help)
    - 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)
  - Neurostimulation
    - ECT, rTMS
  - Consider complimentary and alternative therapies
  - Consider referral