PRACTICAL MANAGEMENT OF MDD

Jon-Paul Khoo

Objectives

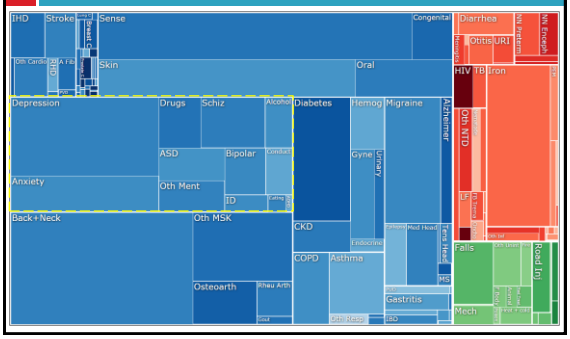
- MDD is a critical public health problem
- MDD in women
- Treatment-resistant depression
  - What is it really
  - Evidence-based management options when first-line antidepressant treatment fails
- Summary

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 a leading cause of worldwide disease burden in women

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

A practice review

- "What is treatment resistance really?"
- Database review of patients
  - With a primary referral diagnosis of unipolar MDD
  - Failure to achieve remission with $\geq$ 2 adequate antidepressant trials
- 328 consecutive non-remitted depressed 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%

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.

2016 CANMAT Clinical Guideline MDD

Table 3. Summary Recommendations for Antidepressants.

Antidepressant (Brand Name(s))	Mechanism	Dose Range
First line (Level 1 Evidence)		
Agomelatine[a] (Valdoxan)	MT_1 and MT_2 agonist; $5\text{-}HT_2$ antagonist	25-50 mg
Bupropion (Wellbutrin)[b]	NDRI	150-300 mg
Citalopram (Celexa, Cipramil)	SSRI	20-40 mg
Desvenlafaxine (Pristiq)	SNRI	50-100 mg
Duloxetine (Cymbalta)	SNRI	60 mg
Escitalopram (Cipralex, Lexapro)	SSRI	10-20 mg
Fluoxetine (Prozac)	SSRI	20-60 mg
Fluvoxamine (Luvox)	SSRI	100-300 mg
Mianserin[c] (Tolvon)	α_2-Adrenergic agonist; $5\text{-}HT_2$ antagonist	60-120 mg
Milnacipran[d] (Ixel)	SNRI	100 mg
Mirtazapine (Remeron)[c]	α_2-Adrenergic agonist; $5\text{-}HT_2$ antagonist	15-45 mg
Paroxetine (Paxil)[d]	SSRI	20-50 mg 25-62.5 mg for CR version
Sertraline (Zoloft)	SSRI	50-200 mg
Venlafaxine (Effexor)[e]	SNRI	75-225 mg
Vortioxetine (Brintellix, Trintellix)[f]	Serotonin reuptake inhibitor; $5\text{-}HT_{1A}$ agonist; $5\text{-}HT_{1B}$ partial agonist; $5\text{-}HT_{1D}$, $5\text{-}HT_{3A}$, and $5\text{-}HT_7$ antagonist	10-20 mg
Second line (Level 1 Evidence)		
Amitriptyline, clomipramine, and others	TCA	Various
Levomilnacipran (Fetzima)[f]	SNRI	40-120 mg
Moclobemide (Manerix)	Reversible inhibitor of MAO-A	300-600 mg
Quetiapine (Seroquel)[g]	Atypical antipsychotic	150-300 mg
Selegiline transdermal[h] (Emsam)	Irreversible MAO-B inhibitor	6-12 mg daily transdermal
Trazodone (Desyrel)	Serotonin reuptake inhibitor; $5\text{-}HT_2$ antagonist	150-300 mg
Vilazodone (Vibryd)[i]	Serotonin reuptake inhibitor; $5\text{-}HT_{1A}$ partial agonist	20-40 mg (titrate from 10 mg)
Third line (Level 1 Evidence)		
Phenelzine (Nardil)	Irreversible MAO inhibitor	45-90 mg
Tranylcypromine (Parnate)		20-60 mg
Reboxetine[j] (Edronax)	Noradrenaline reuptake inhibitor	8-10 mg

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

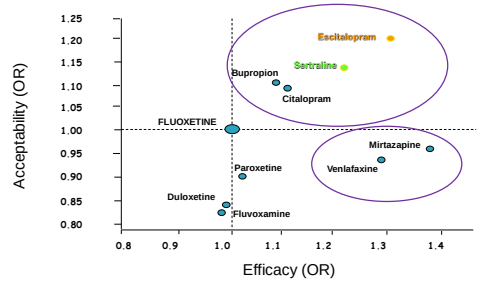
Acute antidepressant treatment
Level 1 evidence

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

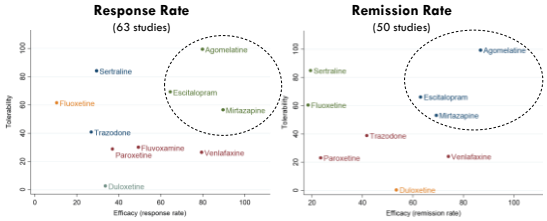


Adapted from: Cipriani A et al. Lancet. 2009 28;373(9665):746-58.

Antidepressant efficacy vs tolerability

23

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
- rTMS
  - 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 — Repetitive Transcranial Magnetic Stimulation
- rTMS
  - 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