MENTAL HEALTH IN GENERAL PRACTICE 2018

MAJOR DEPRESSIVE DISORDER: COMMON QUESTIONS…

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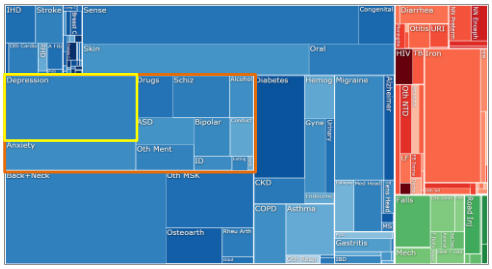
Healthed 19 June 2018

Contents

- Why are we talking about depression?
- What is evidence-based first line treatment for MDD?
- Do antidepressants work?
- Are some antidepressants better than others?
- What do I do when my patient doesn't get better?
- How do I get the best outcome for my depressed patients?

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.



Why are we talking about depression?

- MDD is a critical public health problem
  - Common
  - Severe
  - Recurrent
  - Chronic
  - Disabling
  - Costly
  - Non-remission is the norm

Kovacs M. J Am Acad Child Adolesc Psychiatry. 1996;35:705-715. Kessler RC et al. JAMA. 2003; 289:3095-3105. 3. Kessler RC et al. Arch Gen Psychiatry 1994;51:8-19. Kessler RC et al. Psychol Med. 2010;40:225–37. Kessler RC et al. Arch Gen Psychiatry. 2005;62:617–27. Greenberg PE et al. J Clin Psychiatry 1993;54:405–418. Greenberg PE et al. J Clin Psychiatry 2003;64:1465–74. WHO. Depression Fact Sheet. Geneva: World Health Organization 2017. http://www.who.int/mediacentre/factsheets/fs369/en/ Worden D et al. Curr Psychiatry Rep. 2007 Dec;9(6):449-59.

Why are we talking about depression?

- Primary care is our mental health system for high prevalence psychiatric disorder
  - Up to 80% of all depression management occurs in primary care
  - One of the most common conditions in primary care
    - 10% of primary care patients meet criteria (1)
    - In Australian GP practices the presentation of depression is slightly less common than URTI presentation (2)

1. Craven M et al. Can J Psychiatry 2013; 58(8): 442-448.
2. Cooke G et al. AFP 2013; 42(1): 65-68.

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What is first line treatment for MDD?

- Evidence-based initial treatment
  - Mild-moderate MDD
    - Non-pharmacological treatments
      - "Watchful waiting"; aerobic exercise; psychoeducation; problem-solving; supportive counselling; guided CBT-based self-help
      - Specific psychological treatments

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.

What is first line treatment for MDD?

- Evidence-based initial treatment
  - Mild-moderate MDD
    - Non-pharmacological treatments
      - "Watchful waiting"; aerobic exercise; psychoeducation; problem-solving; supportive counselling; guided CBT-based self-help
      - Specific psychological treatments
      - No empirical evidence supports the preference of non-pharmacological therapies over antidepressants for the acute treatment of major depression

What is first line treatment for MDD?

- Evidence-based initial treatment
  - Moderate-severe MDD
    - Active treatment recommended in all cases
      - As per mild-moderate depression
      - Offer antidepressants in all cases
    - Regular monitoring for improvement, intolerance, suicidal ideation
    - Continue antidepressant therapy
      - 1 year after an initial episode
      - 3+ years if recurrent or particularly severe or concerning (eg psychotic)

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

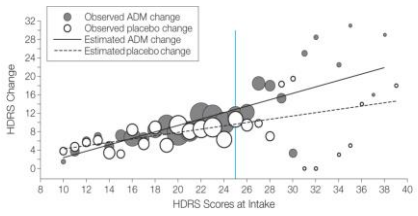
What is first line treatment for MDD?

- Evidence-based initial treatment
  - Mild-moderate MDD
    - Non-pharmacological treatments
    - Specific psychological treatments
  - Moderate-severe MDD
    - PLUS Antidepressant medication

Antidepressant effects and depression severity

A patient-level meta-analysis

Fournier *et al*, JAMA. 2010;303(1):47-53.



Antidepressant discussion approach

- Most people note improvement from 10-14 days
- Expected outcome
- Side-effects
- Many people need to try a number of treatments
- Don't stop just because you start to feel better
- Non-addictive, but unpleasant if abruptly discontinued
- Interactions

What is first line treatment for MDD?

- Evidence-based initial treatment
  - Mild-moderate depression
    - Non-pharmacological treatments
    - Specific psychological treatments
  - Moderate-severe depression
    - PLUS Antidepressant medication
      - Which antidepressant?

Which antidepressant?

- Level 1 evidence supports all of the following antidepressants
- RANZCP acute antidepressant treatment recommendations
  - First-line: SSRI; NDRI; NaSSA; NRI; agomelatine
  - Second-line: SNRI; TCA; SM
  - Third-line: MAOI; RIMA

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

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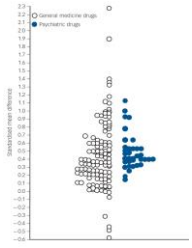
Do antidepressants work?

- What is an adequate outcome measure in treating depression?
  - RCT response?
  - Remission and functional recovery
  - What patients want (1)
    - Presence of positive mental health (optimism, vigour, self-confidence)
    - Feeling like your usual, normal self
    - Return to usual level of functioning at work, home or school
    - Feeling in emotional control
    - Participating in and enjoying relationships with family and friends
    - Absence of symptoms of depression

1. Zimmerman M et al. Am J Psychiatry 2006; 163:148-150.

Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses

Summary of effect sizes



Leucht S, et al. BJP 2012. 200 (2) 97-106.

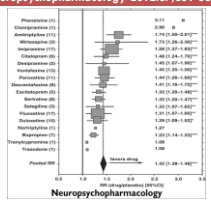
Do antidepressants work?

- Acute antidepressant efficacy is well proven by a huge number of RCTs
  - Drug-placebo differences
    - 15-20% response differences
    - 10-15% remission differences

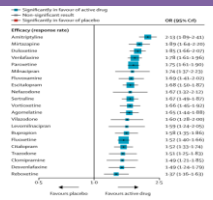
Baghai TC et al. World J Biol Psychiatry. 2006;7(4):198-222.
Bauer M et al. World J Biol Psychiatry. 2007;8(2):67-104.
Sartorius N, et al. Int J Neuropsychopharmacol. 2007 Dec;10 Suppl 1:S1-207.
APA: MDD Practice guideline Am J Psychiatry 2010; 167(10) Suppl:1–117.

Meta-analyses of antidepressant efficacy

Undurraga J and Baldessarini R. Neuropsychopharmacology 2012;37:851-864.



Cipriani A et al. Lancet 2018; 391: 1357-66.



What is clinically meaningful efficacy?

- It is insufficient to know that a difference between active treatment and control is statistically significant?
  - It is clinically relevant to appreciate the magnitude of the difference: how great is the benefit?
- The British National Institute of Clinical Excellence (NICE) propose that the threshold for clinical significance in antidepressant efficacy trials is a NNT of at least 10 (ie 10% difference in response or remission rates)
- Meta-analyses
  - Acute (75 RCTs; 12,000+ patients; SSRI, TCA or placebo): NNT = 5 (1)
  - Maintenance (31 RCTs; up to 36 months): NNT~4-5 (2)

1. Walsh BT, et al. JAMA. 2002 Apr 10;287(14):1840-7.
2. Geddes JR et al. Lancet. 2003 Feb 22;361(9358):653-61.

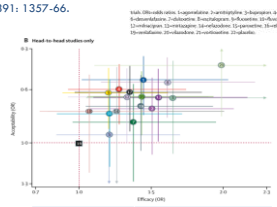
Contents

Comparative efficacy

- There are statistically significant differences in antidepressant efficacy

Efficacy and acceptability of 21 antidepressants

Cipriani A et al. Lancet 2018; 391: 1357-66.



Least efficacious	Most efficacious
Fluoxetine	Agomelatine
Fluvoxamine	Amitriptyline
Reboxetine	Escitalopram
Trazodone	Mirtazapine
	Paroxetine
	Venlafaxine
	Vortioxetine

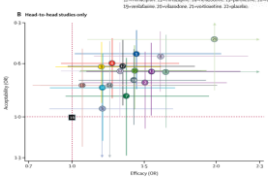
Comparative efficacy

- There are statistically significant differences in antidepressant efficacy
  - But these are small in magnitude and of questionable clinical relevance and do not translate into substantial clinical differences
- …because RCT patients are not "real world" patients
- However, differences exist between antidepressants in speed of onset and tolerability

Efficacy and acceptability of 21 antidepressants

Cipriani A et al. Lancet 2018; 391: 1357-66.

Most Acceptable	Agomelatine Citalopram Escitalopram Fluoxetine Sertraline Vortioxetine
Least acceptable	Amitriptyline Clomipramine Duloxetine Fluvoxamine Reboxetine Trazadone Venlafaxine



Least efficacious	Most efficacious
Fluoxetine Fluvoxamine Reboxetine Trazadone	Agomelatine Amitriptyline Escitalopram Mirtazapine Paroxetine Venlafaxine Vortioxetine

Comparative efficacy

- Small differences do exist between antidepressants in RCT efficacy
- There are statistically significant differences in antidepressant efficacy, but these are small and of questionable clinical relevance and do not translate into substantial clinical differences
- …because RCT patients are not "real world" patients
- However, differences exist between antidepressants in speed of onset and tolerability
- Effectiveness studies consider real world utility

Contents

Why does MDD not get better?

A practice review

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

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

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

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?

A practice review

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%

When depression fails to remit

- Consider "pseudo-resistance"
- Treat non-remitting disease

When depression fails to remit

- Consider "pseudo-resistance"
  - Establish an accurate initial diagnosis
    - Reassessment
    - Consider longitudinal status and functioning
    - Consider life-events
    - Consider personality
    - Rule out
      - Disorder due to a general medical condition
      - Disorder due to direct effects of a substance
    - Consider challenging depressive subtypes and specific treatment needs

When depression fails to remit

- Consider "pseudo-resistance"
  - Establish an accurate initial diagnosis
  - Identify and treat comorbidity
  - Ensure adequate initial treatment
    - Adequate dose
    - Adequate duration
      - Response usually in 2 weeks, minimum 3 weeks, remission usually requires 6+ weeks
    - Adherence
    - Maximise tolerability; education; strategies for managing side-effects (esp. sexual dysfunction, weight gain, insomnia, and somnolence); monitoring; compliance aids

When depression fails to remit

- Consider "pseudo-resistance"
- Treat non-remitting disease
  - Specific depression-focussed psychological therapy
  - Pharmacotherapy
    - Increase, change or add
  - Neurostimulation
  - (Complimentary and alternative therapies)
  - (Consider experimental therapies)

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Take home messages for optimising MDD treatment

- Minimise "pseudo-resistance" from the outset
  - Establish an accurate initial diagnosis
  - Identify and treat comorbidity
  - Ensure adequate initial treatment
- Mild-moderate MDD management
  - Non-pharmacological treatments
  - Specific psychological treatments
- Moderate-severe MDD management
  - PLUS antidepressant

Take home messages for optimising MDD treatment

- Non-remitting MDD
  - Reassess for "pseudo-resistance"
  - Treat non-remitting disease
    - Specific depression-focussed psychological therapy
    - Increase, change or add pharmacotherapy
    - Neurostimulation
    - Consider complimentary and alternative therapies
    - Consider experimental therapies