Update on Depression and Trauma

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RAMSAY MENTAL HEALTH
People caring for people
RAMSAY HEALTH CARE

THE UNIVERSITY OF MELBOURNE

Disclosures

Professor Hopwood has the following relationships to disclose:

- **Speaker's Fees / Honoraria**
  Astra-Zeneca, Eli-Lilly, Janssen- Cilag, Lundbeck, , Servier,
- **Advisory Board**
  Eli Lilly, Lundbeck,
- **Travel Support**
  Astra-Zeneca,, Bionomics,Eli-Lilly, Janssen- Cilag, Lundbeck, Servier
- **Clinical trials/Research support**
  Astra-Zeneca, Bionomics, Bristol-Myers Squibb, Cephalon, Eli-Lilly, Forrest, ISSCR, Lundbeck, NHMRC, Servier, Sunovion, VNI,
- **Board Member**
  Fenix, RANZCP, Summer Foundation

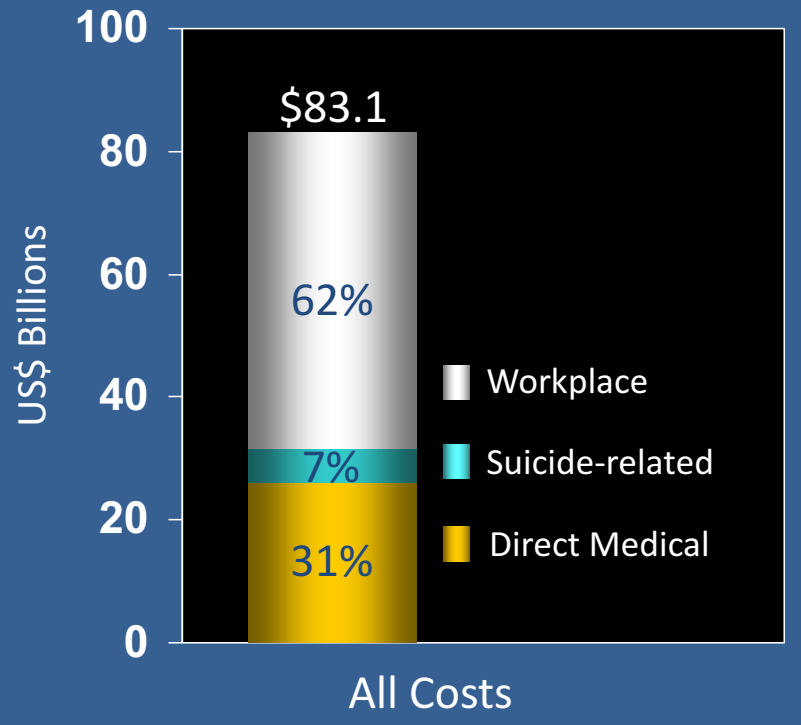
MDD is Disabling and an Economic Burden Worldwide

Disability[1]

Rank*	1990	2020 (est.)
1	Lower respiratory infections	Ischemic heart disease
2	Diarrheal diseases	Major depressive disorder
3	Perinatal conditions	Road traffic accidents
4	Major depressive disorder	Cerebro-vascular disease
5	Ischemic heart disease	Chronic obstructive pulmonary disease

*Rank based on a composite measure of Disability-Adjusted Life Year (DALY) in 15-44 year olds

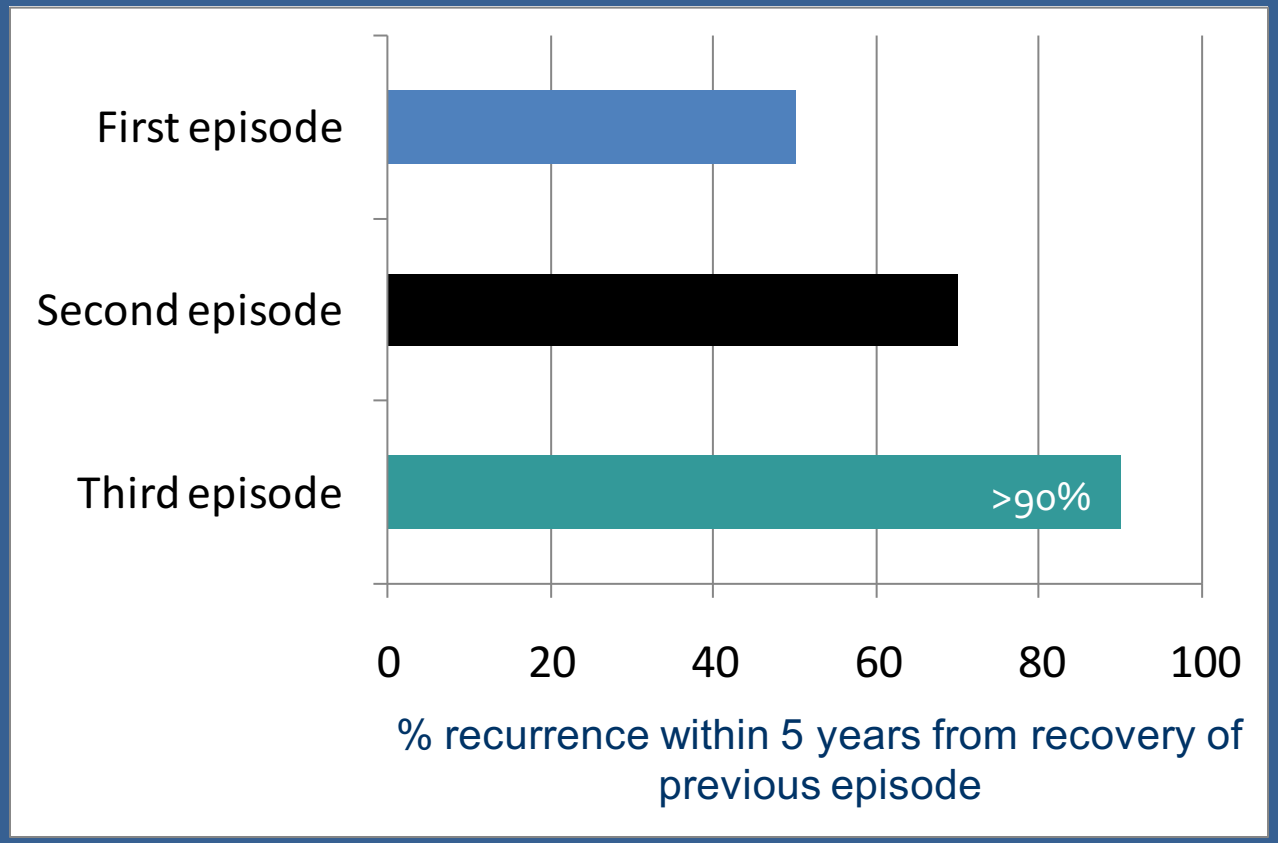
Economic Burden of MDD[2]
US (2000)



2. Greenberg PE, et al. *J Clin Psychiatry*. 2003;64(12):1465-1475.
1. Murray CJ, et al. *Science*. 1996;274(5288):740-743.

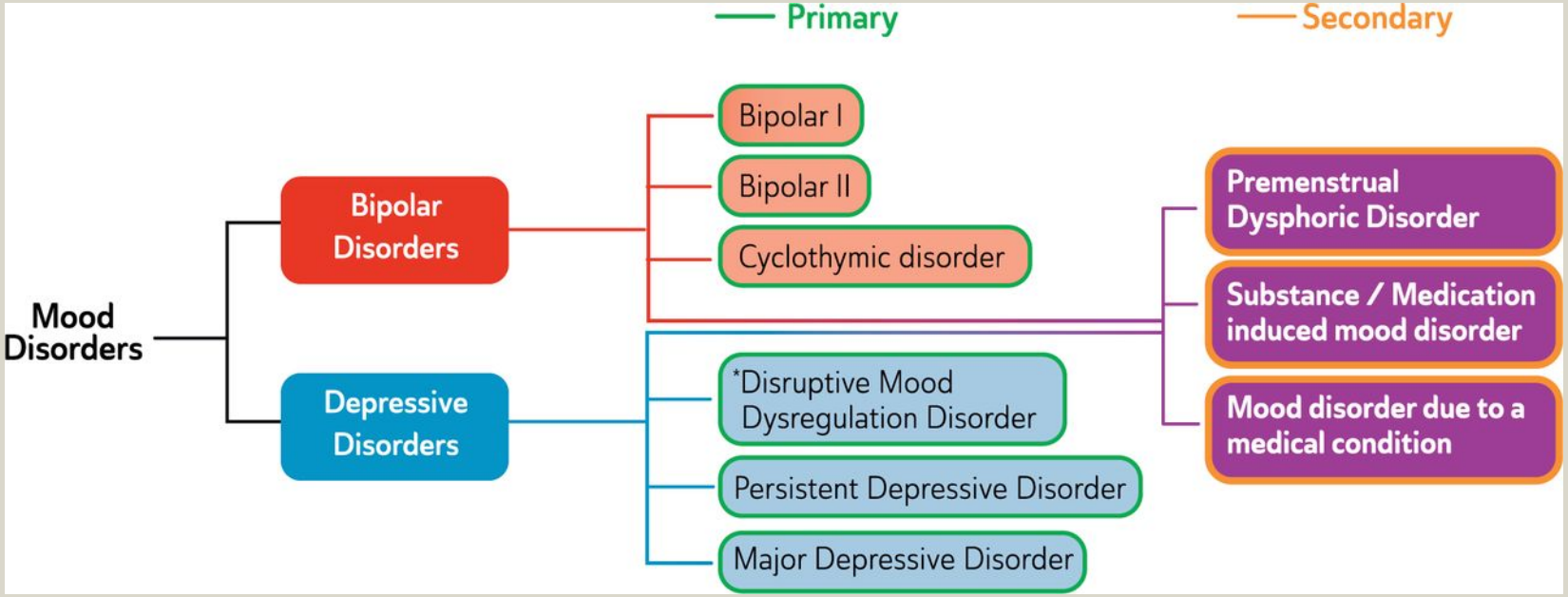
Major Depression – Course and Prognosis

Prospective Follow up of 318 patients



Keller and Boland 1996

CLASSIFICATION OF MOOD DISORDERS
DSM-5



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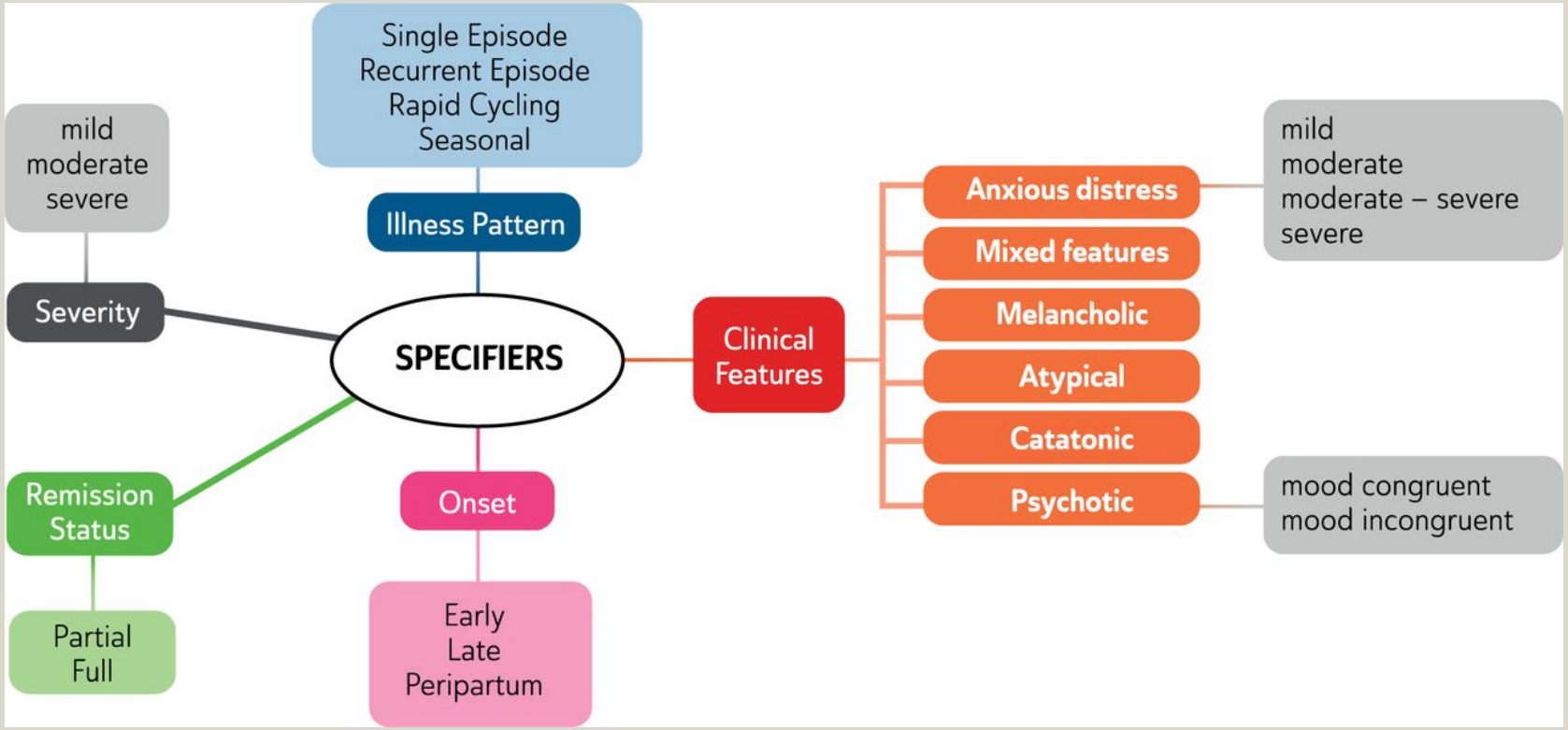
MOOD DISORDERS SPECIFIERS



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DSM 5 Mixed State Specifier

- Present for both Bipolar and depressive Disorders
  - Requires full criteria for one pole plus 3 of the symptoms of the opposing pole
  - Opposing pole symptoms must be observable to others
  - If full criteria for both are met, diagnosis is mania with mixed features

Scope of Problem

- In Australia, depression and anxiety affect a substantial proportion of the population (4.8% of men and 10% of women) and is responsible for 8% of the total loss in disability-adjusted life years.
- It is the top-ranking cause of non-fatal disease in the Australian community for women, and is also associated with an increased risk of ischaemic heart disease and suicide, both causes of early death.
- Best estimates are that 55% of patients with Depression go untreated
- Models of Stepped care are an evolving priority

A Recommendation

US Preventive Services Task Force 2016

- Reviewed benefits and harms of Screening for depression in
  - Adult populations
  - Including older adults and pregnant and postpartum women
- Reviewed the accuracy of depression screening instruments
- Benefits and Harms of Depression treatment

A Recommendation

US Preventive Services Task Force 2016

Does Adding Screening Improve Outcomes?

- Identified 9 good or fair quality trials only
  - 5 in general adults n=2924
  - 4 in older adults n=890
- Only 1 RCT of screening versus TAU (Williams et al Am J Med 1999)
  - Detection Impact
    - 39% with 20 item questionnaire V 29% TAU N.S.
    - Mainly picked up more mild cases
  - Treatment Impact
    - Recovery from depression was more likely in the case-finding than usual care groups, 32/67 (48%) versus 8/30 (27%, *P* = 0.03)

A Recommendation

US Preventive Services Task Force 2016

Key recommendations

For all adults over the age of 18, Screen for depression, with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow up

Risk is low, refer to PHQ9 and 2, HADS, GDS and EDS

Acknowledge there is no data on when and how often

Describe the net benefit as moderate

A Response

- Not applicable in Australia
- Need to focus on appropriate care pathway
- ?Reduce effort for clinical diagnosis
- Get stepped care pathway right first
- Noted RANZCP Guidelines did not recommend screening

Hopwood and Malhi MJA 2016

ANZJP

Australian & New Zealand Journal of Psychiatry
1–122
DOI: 10.1177/0004867415617657

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Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders

Gin Malhi[1,2,3], Darryl Bassett[1,4,5], Philip Boyce[1,6], Richard Bryant[1,7], Paul Fitzgerald[1,8], Kristina Fritz[1,9], Malcolm Hopwood[1,10], Bill Lyndon[1,11,12,13], Roger Mulder[1,14], Greg Murray[1,15], Richard Porter[1,14] and Ajeet B Singh[1,16]

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Abstract

Objectives: To provide guidance for the management of mood disorders, based on scientific evidence supplemented by expert clinical consensus and formulate recommendations to maximise clinical salience and utility.

Methods: Articles and information sourced from search engines including PubMed and EMBASE, MEDLINE, PsycINFO and Google Scholar were supplemented by literature known to the mood disorders committee (MDC) (e.g., books, book chapters and government reports) and from published depression and bipolar disorder guidelines. Information was reviewed and discussed by members of the MDC and findings were then formulated into consensus-based recommendations and clinical guidance. The guidelines were subjected to rigorous successive consultation and external review involving: expert and clinical advisors, the public, key stakeholders, professional bodies and specialist groups with interest in mood disorders.

Results: The Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (Mood Disorders CPG) provide up-to-date guidance and advice regarding the management of mood disorders that is informed by evidence and clinical experience. The Mood Disorders CPG is intended for clinical use by psychiatrists, psychologists, physicians and others with an interest in mental health care.

Conclusions: The Mood Disorder CPG is the first Clinical Practice Guideline to address both depressive and bipolar disorders. It provides up-to-date recommendations and guidance within an evidence-based framework, supplemented by expert clinical consensus.

KEY FEATURES OF THE CLINICAL PRACTICE GUIDELINE FOR MOOD DISORDERS

The Royal Australian & New Zealand College of Psychiatrists

- Brings together all mood disorders (major depression and bipolar disorder) into 1 guideline
  - Shared key elements
- Follows DSM-5 classification
  - Limitations of the system recognised
- Emphasis on a BioPsychoSocial and Lifestyle (BPSL) aetiological perspective
  - Encourages Formulation to guide treatment (not DSM diagnosis)
- Limitations of the evidence base in depression and bipolar trials stated upfront
- Uses the NHMRC evidence levels
- Consensus Based Recommendations (CBR) used in addition to Evidence-based Recommendations (EBR)
  - Considerable debate in formulating the CBRs – Delphi approach used

THE BIO PSYCHO SOCIAL LIFESTYLE MODEL

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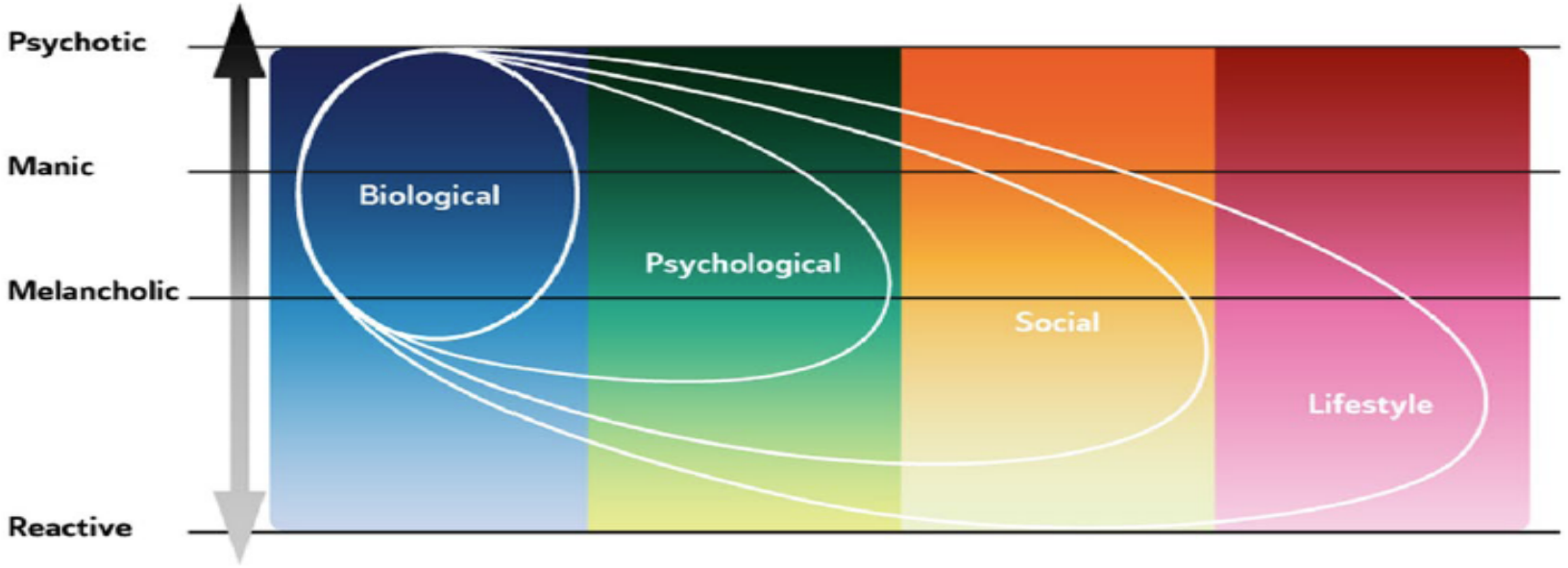

Biological Treatments	Psychological Treatments	Social Treatments	Lifestyle Treatments
· Antidepressants · Antipsychotics · Mood stabilisers · Electroconvulsive therapy · Transcranial magnetic stimulation	· Brief cognitive behavioural therapy · Formal cognitive behavioural therapy · Interpersonal therapy · Mindfulness · Acceptance and commitment therapy · Schema therapy	· Family psychoeducation · Family / friends · Formal support groups · Community groups · Caregivers · Employment · Housing	· Exercise · Diet · Smoking cessation · Alcohol cessation · Ceasing drugs · Managing substance misuse · Sleep

MANAGEMENT OF DEPRESSION

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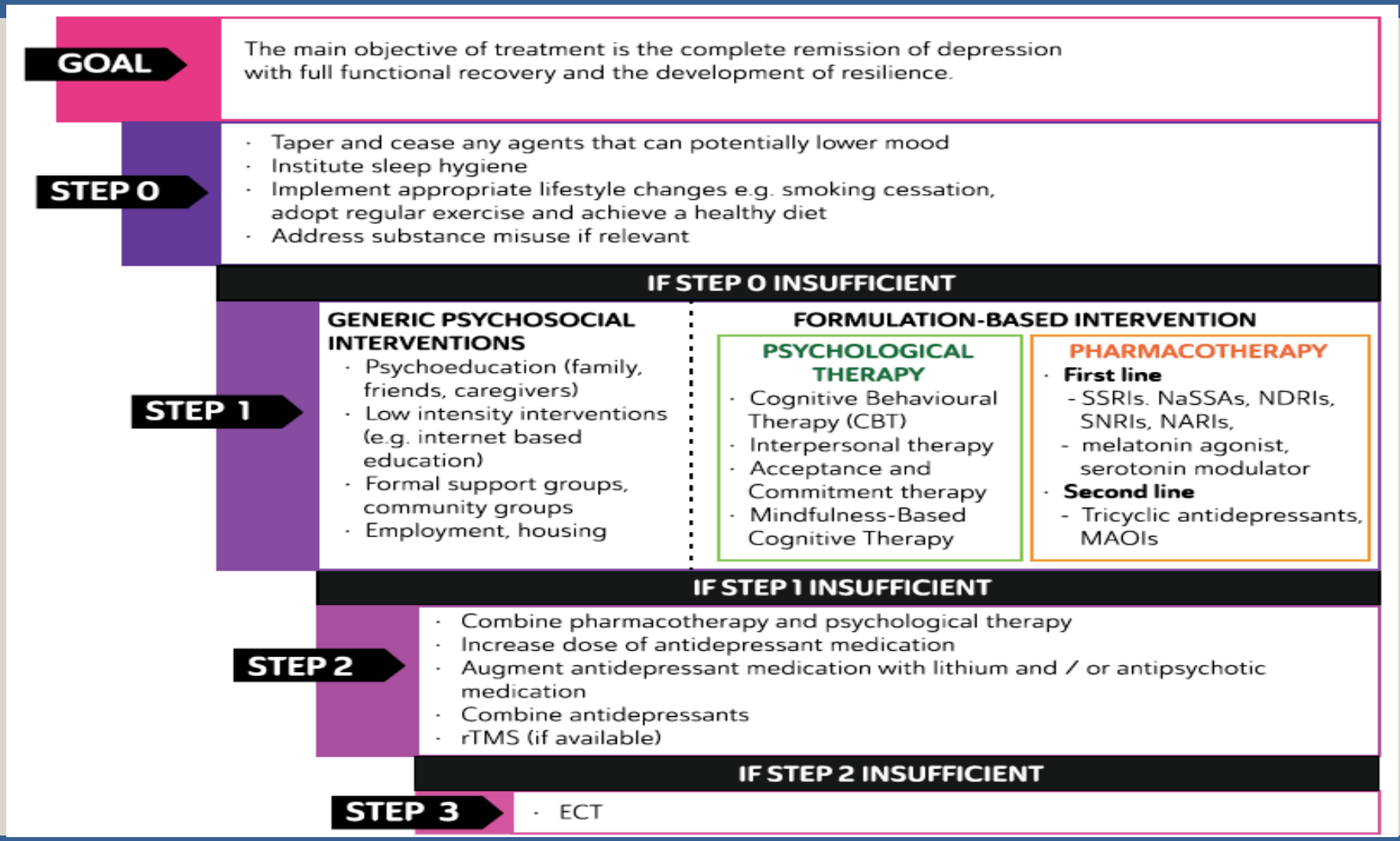

COMMON PSYCHOTHERAPIES FOR TREATMENT OF DEPRESSION

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CBT Cognitive-behavioural therapy (CBT) aims to modify dysfunctional cognitions and related behaviours that are presumed to maintain depression. Amongst evidence-based psychological therapies, CBT is the most widely researched treatment for depression, and it is recommended by all international guidelines (NICE, 2009; Parikh et al., 2009).

IPT Interpersonal psychotherapy (IPT) is a brief structured approach that addresses interpersonal issues and role transitions. It has Level I evidence for the treatment of major depression. IPT has Level I evidence for both acute depression and depression maintenance/relapse.

MBCT and ***ACT*** Recently developed structured therapies, such as mindfulness-based cognitive therapy (MBCT) and acceptance and commitment therapy (ACT) have not been evaluated as thoroughly as CBT and IPT, but appear to be effective in reducing depressive symptoms and in preventing relapse of depression (specificity for subtype and/or severity of depression remains unclear) (Fjorback et al., 2011). MBCT may be better for patients prone to worry and ACT may be best for patients needing to accept and adjust to persisting problems.

PSYCHOLOGICAL THERAPY FOR MDD	Grade
1.1. Psychological interventions should only be delivered by clinicians trained in the relevant evidence-based approach.	CBR
1.2. Treatment should be guided by a published manual, tailored to the individual, and should pay particular attention to establishing and maintaining the therapeutic alliance.	CBR
1.3. Patients with *mild-moderate depression* should be offered one of the evidence-based psychotherapies as first line treatment.	EBR I
1.4. Patients with *moderate-severe depression* should be offered combined pharmacotherapy and psychotherapy as first line treatment.	EBR I
1.5. Patients with *chronic depressive disorders* should be offered combined psychotherapy and pharmacotherapy as first line treatment.	EBR I

PSYCHOTHERAPIES FOR DEPRESSION ACUTE PHASE AND MAINTENANCE/RELAPSE

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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	+	○
Problem-solving therapy	+	○
Behavioural activation therapy	+	○
Self-control therapy	+	○
Short-term psychodynamic therapy	+	○
Mindfulness-based cognitive therapy (MBCT)	○	+

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

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ANTIDEPRESSANT MEDICATIONS

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Table 13. Summary of antidepressant clinical use – acute.

Typical recommendation[a]	Antidepressant Class	Generic Name of Medication	Principal Mechanism of Action	Features of depression for which antidepressant is most likely to be useful
1st line	SSRI	Citalopram, Escitalopram, Fluvoxamine, Fluoxetine, Paroxetine, Sertraline	Selective 5-HT reuptake blockade	Anxiety
	NARI	Reboxetine[b]	Reuptake inhibitor for noradrenaline and adrenaline	Activation (e.g., motivation & withdrawal)
	NaSSA	Mirtazapine Mianserin	Blocks the reuptake of serotonin via 5-HT_{2A} & 5-HT_{2C} receptors. Also blocks $5HT_3$ & Alpha-2 receptors.	Insomnia, circadian disruption, weight loss, reduced appetite
	Melatonergic agonist	Agomelatine	Melatonin agonist (M1 and 2 receptors) and 5-HT_{2C} antagonist	Sleep problems, sexual dysfunction, poor hedonic drive
	NDRI	Bupropion[c]	Blocks the action of the noradrenaline transporter and dopamine transporter	Fatigue
2nd line	SNRI[d]	Desvenlafaxine, Venlafaxine,[e] Duloxetine, Milnacipran	Block both serotonergic and noradrenergic reuptake. Latter leads to an increase in prefrontal dopamine.	Melancholia; severe depression. *Velafaxine*: treatment resistant depression. *Duloxetine*: pain
	TCA	Amitriptyline, Clomipramine, Dothiepin, Imipramine, Nortryptiline Trimipramine Doxepin	Block NA reuptake. Some also block 5-HT reuptake. All TCAs inhibit H_1, $\alpha 1$, & M_1, receptors. Some also block 5-HT_{2C} & 5-HT receptors. Broad spectrum of actions, including blockade of voltage-sensitive sodium channels.	Pain Melancholia
	Serotonin Modulator*	Vortioxetine	5HT1a agonist, 5HT1b partial agonist, 5HT3a and 7 antagonist 5HT transporter inhibitor	Melancholia Severe *depression* Enhances *cognition*
3rd line	MAOI	Phenelzine, Tranylcypromine	Irreversibly inhibit the mitochondrial enzymes MAO-A (metabolises 5-HT, NA & DA) and MAO-B (preferentially metabolises DA)	Melancholia Atypical symptoms[f] Treatment resistant depression
	Reversible MAOI	Moclobemide	Reversible inhibitor of MAO-A (RIMA)	Mild to moderate depression with anxiety
Adjunctive	SARI	Trazodone	Serotonin 2A/2C antagonist and reuptake inhibitor (at high dosage). At low doses blocks 5-HT2A, $\alpha 1$, & H_1 receptors (hypnotic action)	Used when patients do not respond well to 1st line

Notes: (1) SSRI, selective serotonin reuptake inhibitor; NARI, noradrenaline reuptake inhibitor; NaSSA, noradrenaline and specific serotonergic antidepressant; NDRI, noradrenaline-dopamine reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant; SM, serotonin modulator, MAOI, monoamine oxidase inhibitor; SARI, serotonin antagonist and reuptake inhibitor. (2) In New Zealand, certain antidepressants are not funded unless suitable alternatives have been trialled first.

*References: (Boulenger et al., 2012; Citrome, 2015; Katona and Katona, 2014; McIntyre et al., 2014; Mahableshwarkar et al., 2015; Sanchez et al., 2015; Schatzberg et al., 2014).

[a]There is some flexibility in terms of 1st, 2nd, and 3rd treatment, based on patient's symptoms (e.g., MAOIs would be prescribed 1st line for atypical depression); [b]Atomoxetine is prescribed for ADHD and is therefore not recommended 1st line for depression; [c]Only indicated in Australia for smoking cessation; [d]SNRIs have been positioned as 2nd line only because of greater toxicity in overdose; [e]Low dose; [f]Evidence is equivocal Trimipramine: refractory insomnia.

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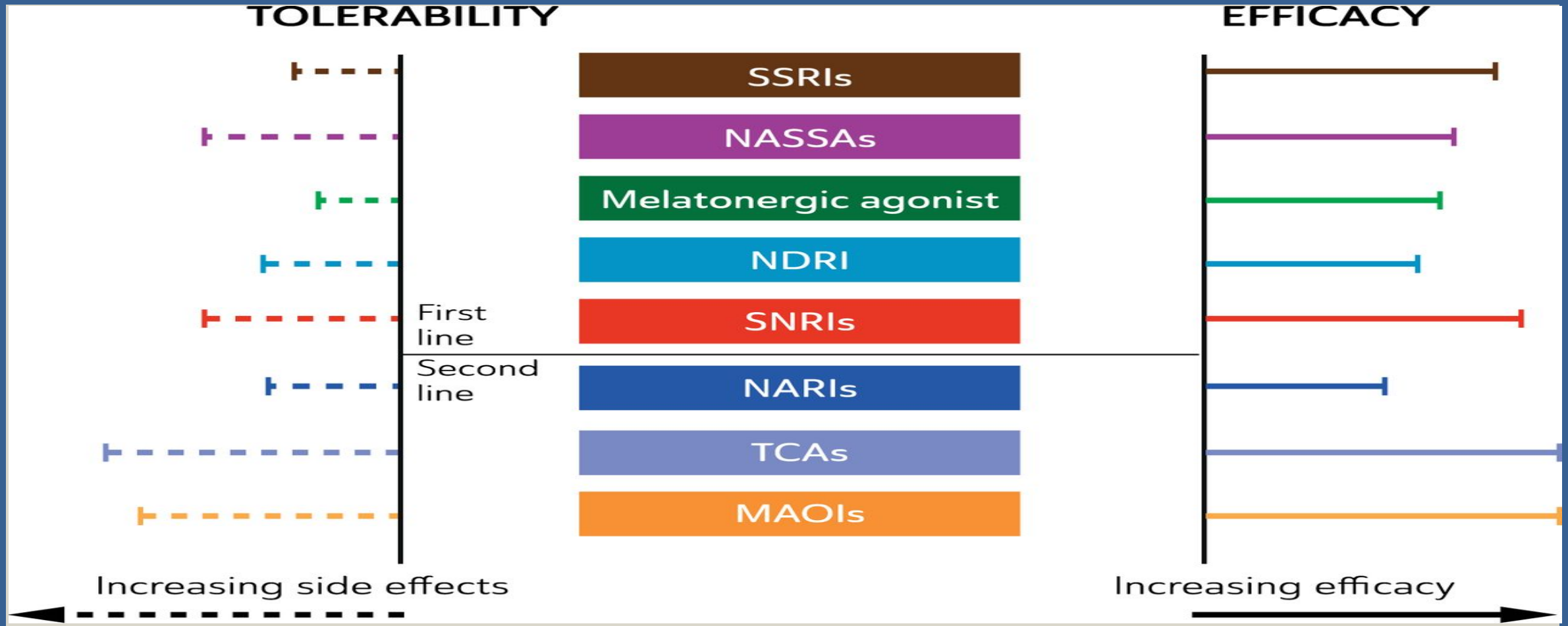
UTILITY OF ANTIDEPRESSANT MEDICATIONS



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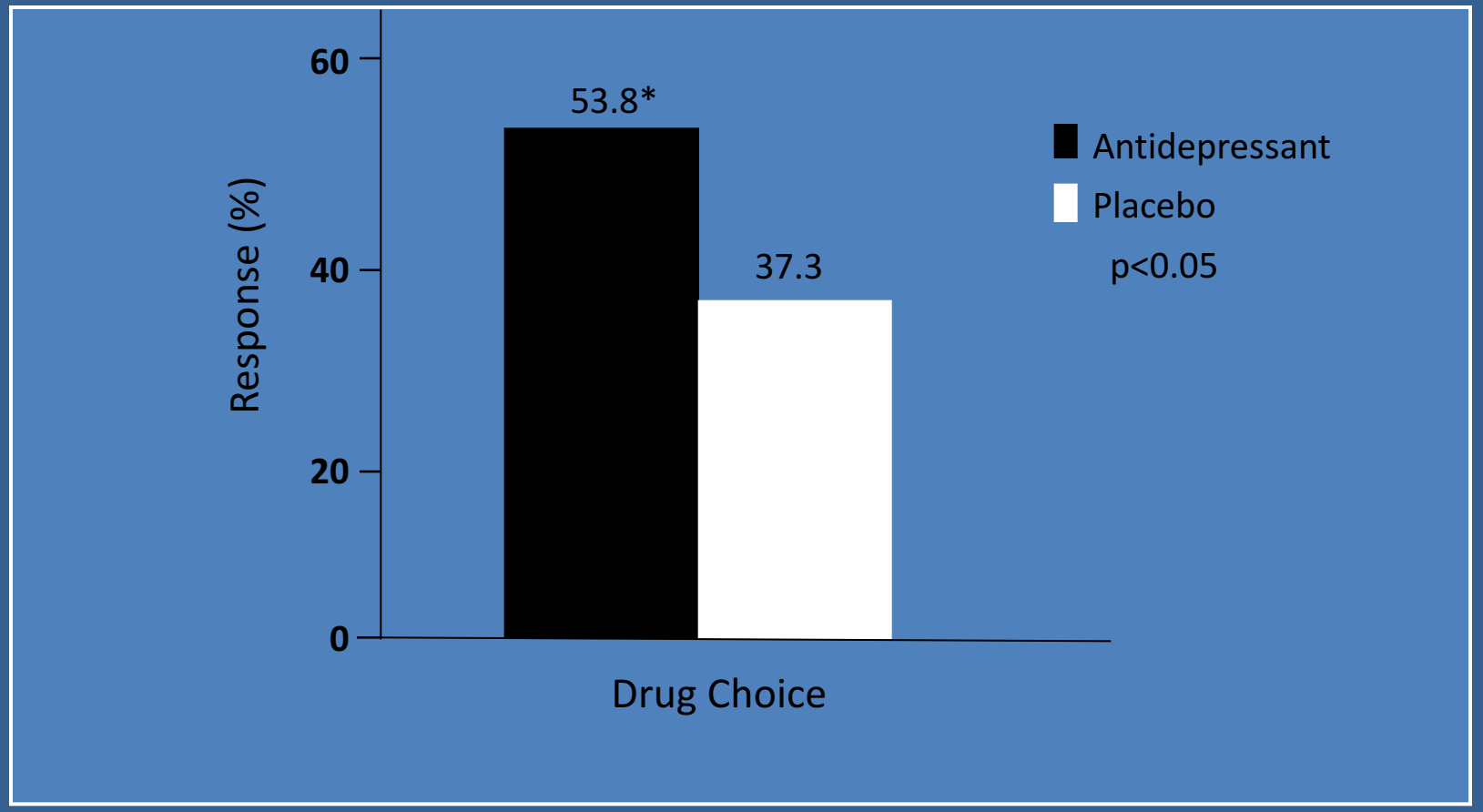
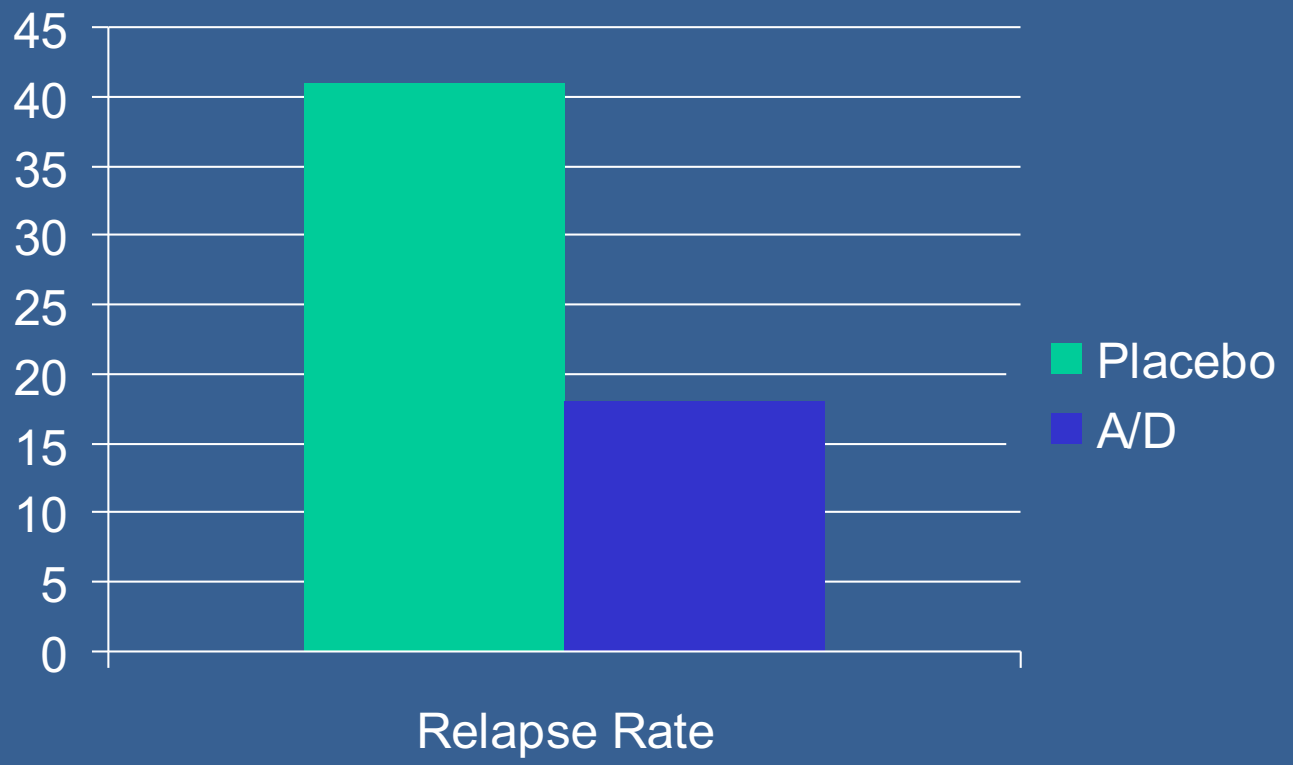
Efficacy?

Antidepressant and Placebo Response Rates
(n=36,385; 262 drug–placebo pair-wise comparisons)



Papakostas et al. *Eur Neuropsychopharmacol* 2009;19(1):34-40. Copyright Elsevier (2009).

Relapse Prevention - Antidepressants



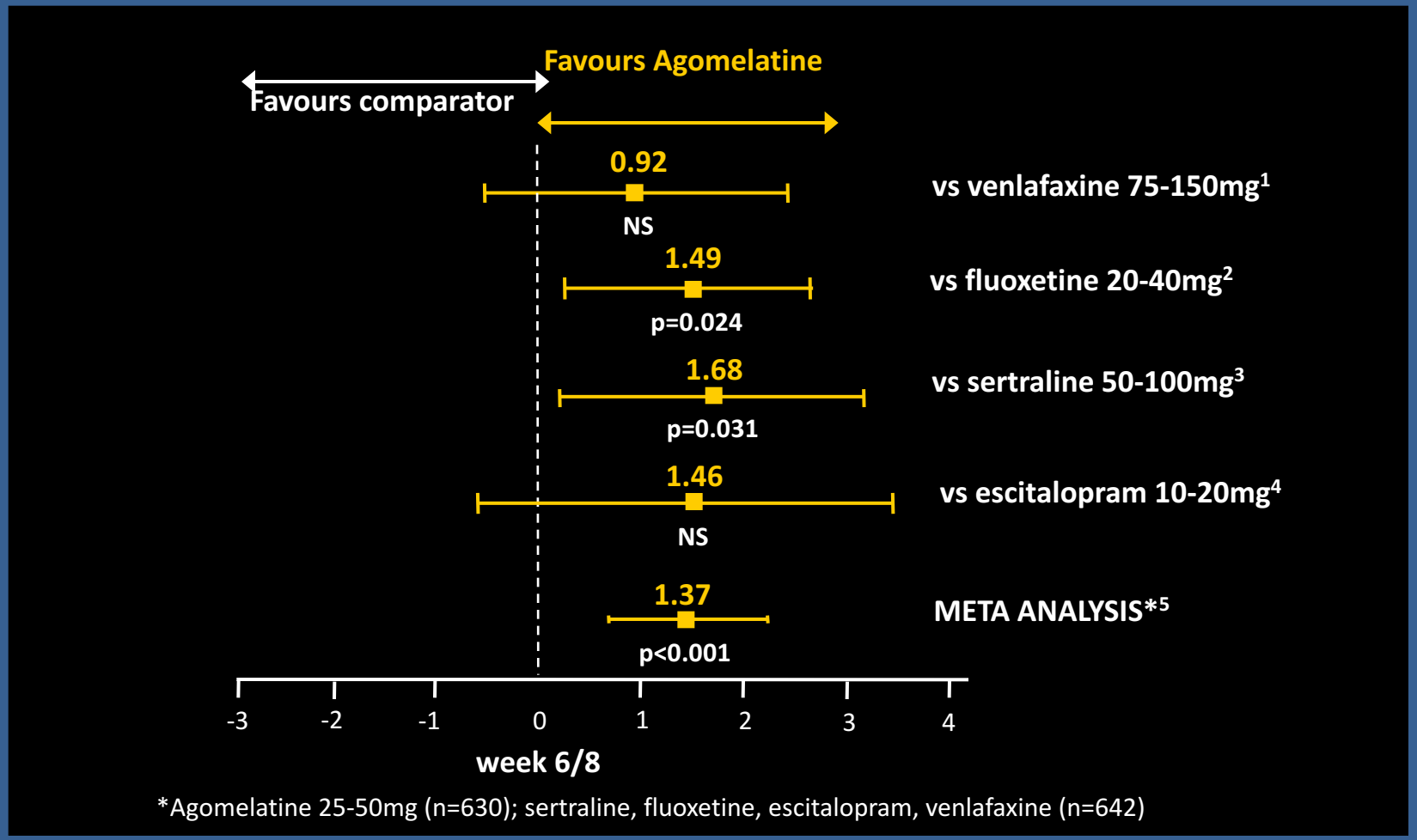
Geddes et al Lancet 2003

Refinements

- Current Antidepressant Mechanisms
  - SNRI; Levomilnacipram
  - Newer Mechanisms; Agomelatine, Vortioxetine
- Atypical Antipsychotics
  - Shifting Indications
  - New Agents; Lurasidone, Brexpiprazole
  - Approved in Australia for Schizophrenia

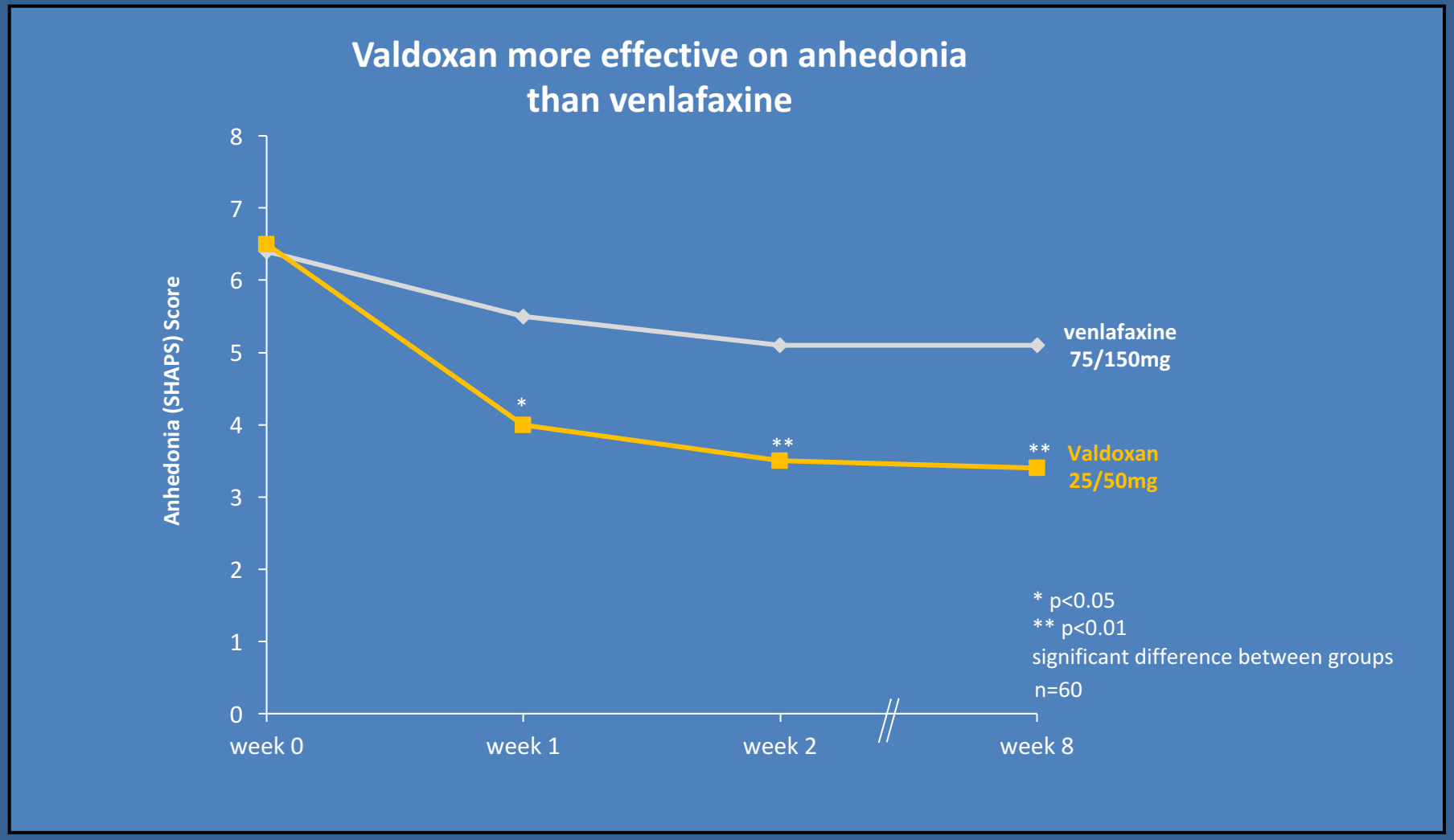
Agomelatine efficacy

Agomelatine versus comparator: summary of HAM-D score differences



1. Lemoine P et al *J Clin Psych* 2007;68:1723-1732 2. Hale A et al *Int Clin Psychopharm* 2010 doi:10.1097/YIC.0bo13e32833a86aa 3. Kasper S et al *J Clin Psych* 2010;71:109-120. 4. Quera Salva M et al *Int J Neuropsych* 2010;13(suppl 1):P03-P043 5. Kasper S et al *Eur Neurosych* 2010

Efficacy on Anhedonia (SHAPS) in MDD:[1] Agomelatine vs Venlafaxine



1. Martinotti G et al *J Clin Psychopharmacol* 2012;32(4):487-491

Patient Perspectives on Outcomes

- Positive mental health *(optimism, vigor, self-confidence)*
- Feeling like normal self
- Usual level of functioning *(work, home, school)*
- Feeling in emotional control
- Enjoying relationships with family and friends
- Absence of symptoms of depression

Modified from Zimmerman et al., *Am J Psychiatry* 2006

New Agents

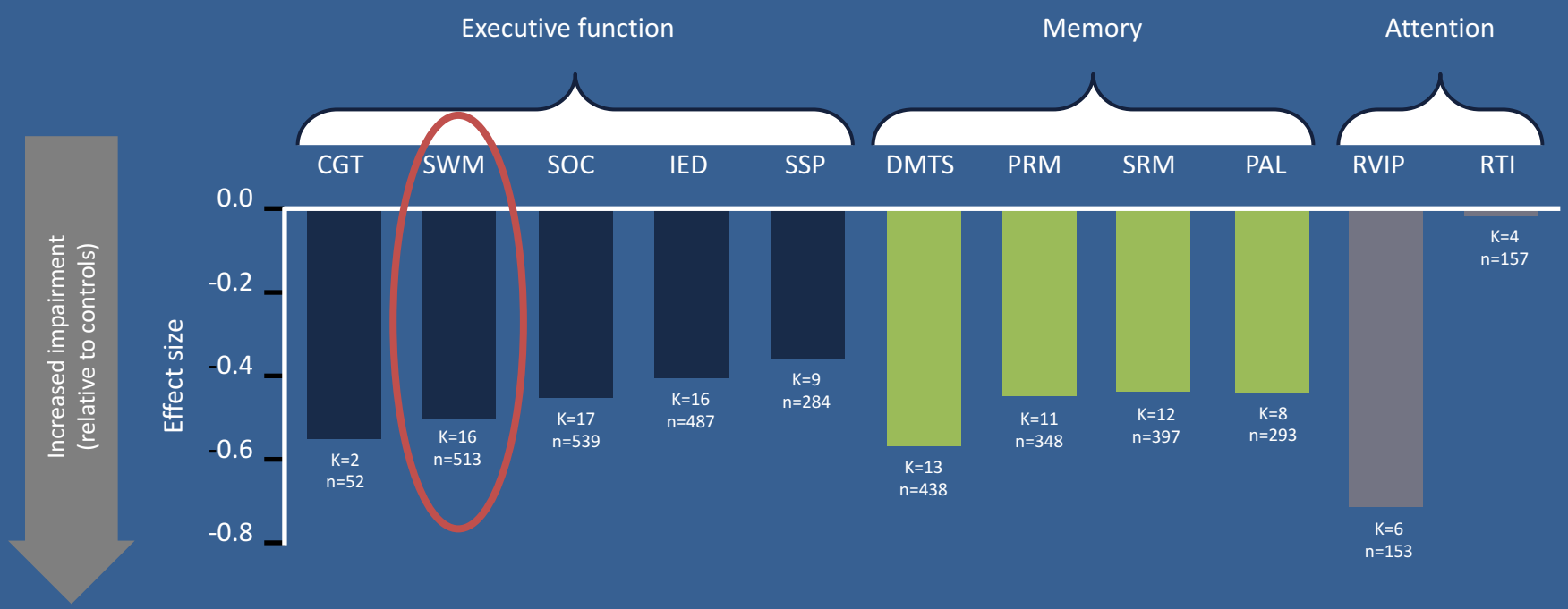
Vortioxetine

- SSRI,5-HT 1A and 1B Partial Agonist,
  5-HT3A Antagonist,5-HT 7 Antagonist
- Multiple Phase 111 Trials published

  Alvarez E, et al. Internat. J. Neuropsychopharm.2011 (5): 1–12.
- Includes an Elderly Depression Study

  Katona C, et al. International clin. Psychopharm. 27 (4): 215–23.
- Appropriate Dose
- ?Cognitive Benefits

'Cold' cognitive impairments in currently depressed patients



A recent meta-analysis indicated that currently depressed patients show impairments in executive function, memory and attention

CGT, Cambridge Gambling Task; SWM, Spatial Working Memory; SOC, Stockings of Cambridge; IED, Intra-Extra Dimensional Set-Shift; SSP, Spatial Span; DMTS, Delayed Matching-to-Sample; PRM, Pattern Recognition Memory; SRM, Spatial Recognition Memory; PAL, Paired Associates Learning; RVIP, Rapid Visual Information Processing; RTI, Response to Intervention

Poster presented at the British Association for Psychopharmacology 2012 Summer Meeting;
see also Rock PL et al. Psychol Med 2013 Oct 29 [Epub ahead of print]

New Agents/Glutamate

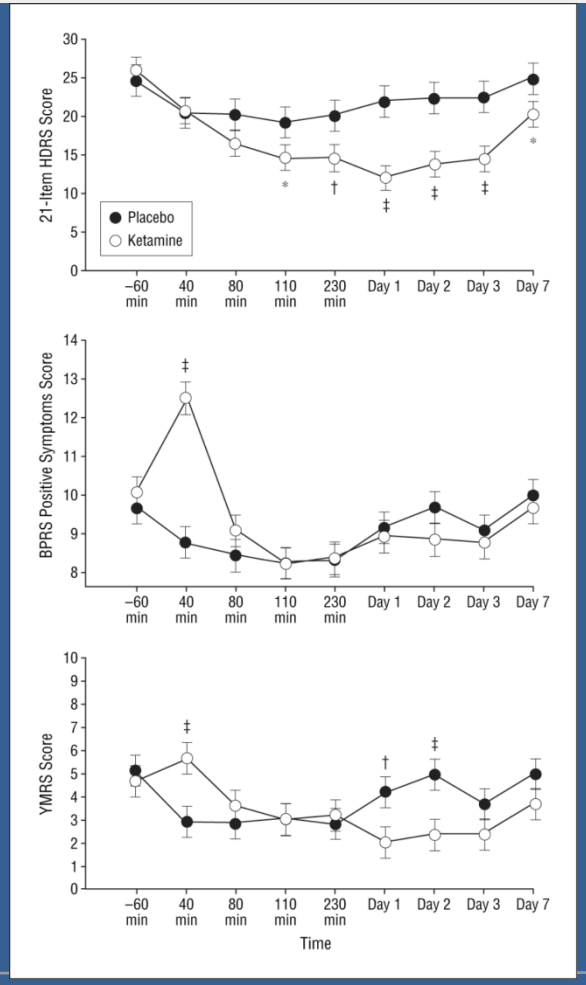
Glutamate

- Long Standing Area of Investigation
- Stimulated by results with Ketamine
- Non competitve high affinity NMDA antagonist
- Some additional dopamine and u-opiod activity

The JAMA Network

From: **A Randomized Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression**

Arch Gen Psychiatry. 2006;63(8):856-864. doi:10.1001/archpsyc.63.8.856



Date of download: 10/4/2013

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New Agents

Natural Medicines

- Extremely Popular
- Tend to be (relatively)
  - Incompletely understood mechanistically
  - Inconsistently manufactured
  - Evaluated at a lower standard
- Are we missing opportunities?
  - Eg L Methyl Folate

New Mechanisms

- ECT
  - Ultra Brief
- MST
- TMS
- DBS

Mental Health Responses To Trauma

- Most people recover with no long term effects
- Some people report long term, extreme distress and social / occupational impairment
- Diagnoses:
  - Depression
  - Substance abuse
  - Anxiety, including panic, phobias, and post-traumatic stress disorder (PTSD)

DSM 5: PTSD – CRITERION A

- exposure to: actual or threatened death, serious injury, or sexual violence, as follows:
  (1 required)

- **Via:**

1. directly experiencing
2. Witnessing in person the event occurring to others
3. Learning that it occurred to a family member or close friend – events violent or accidental
4. Repeated or extreme exposure to aversive details of traumatic events e.g. first responders; other occupational exposures

PTSD

- How many Australians have been exposed to a potentially traumatic event?
- Females - 50%
- Males – 65%
- Examples of PTEs:

combat	other violent crimes
torture	severe accidents
rape victims	natural disasters

PTSD (DSM-5)

- A: Objective experience of trauma
- B: Intrusive memories (images, smells, etc.) (1/5)
- C: Active attempts to avoid reminders (1/2)
- D: Negative alterations in cognitions and mood (2/7)
- E: Hyperarousal, tense, on edge, jumpy (2/6)
- F: Duration > 4 weeks
- G: Functional impairment and/or distress

COMMON PATTERNS OF RESPONSE FOLLOWING TRAUMA OR DISASTER (BONNANO)

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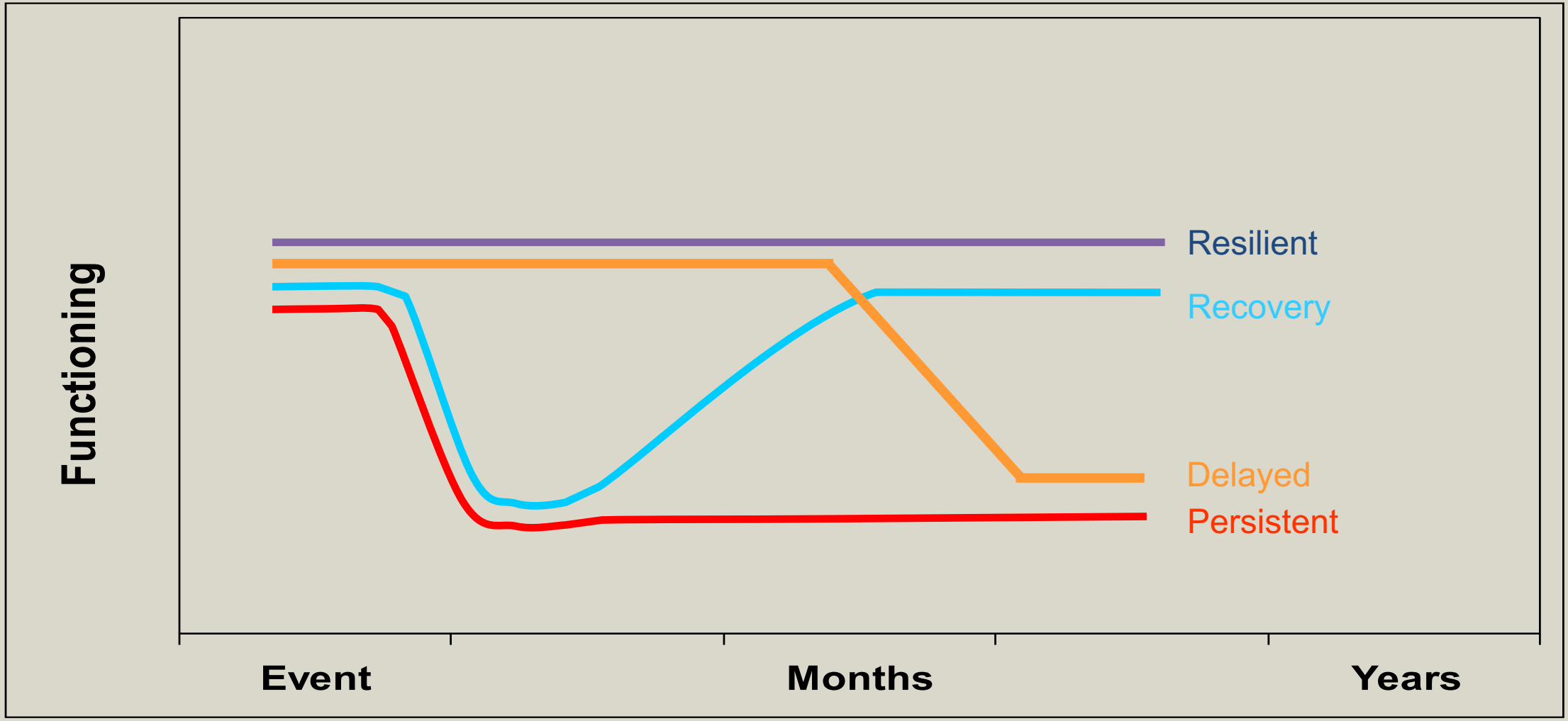


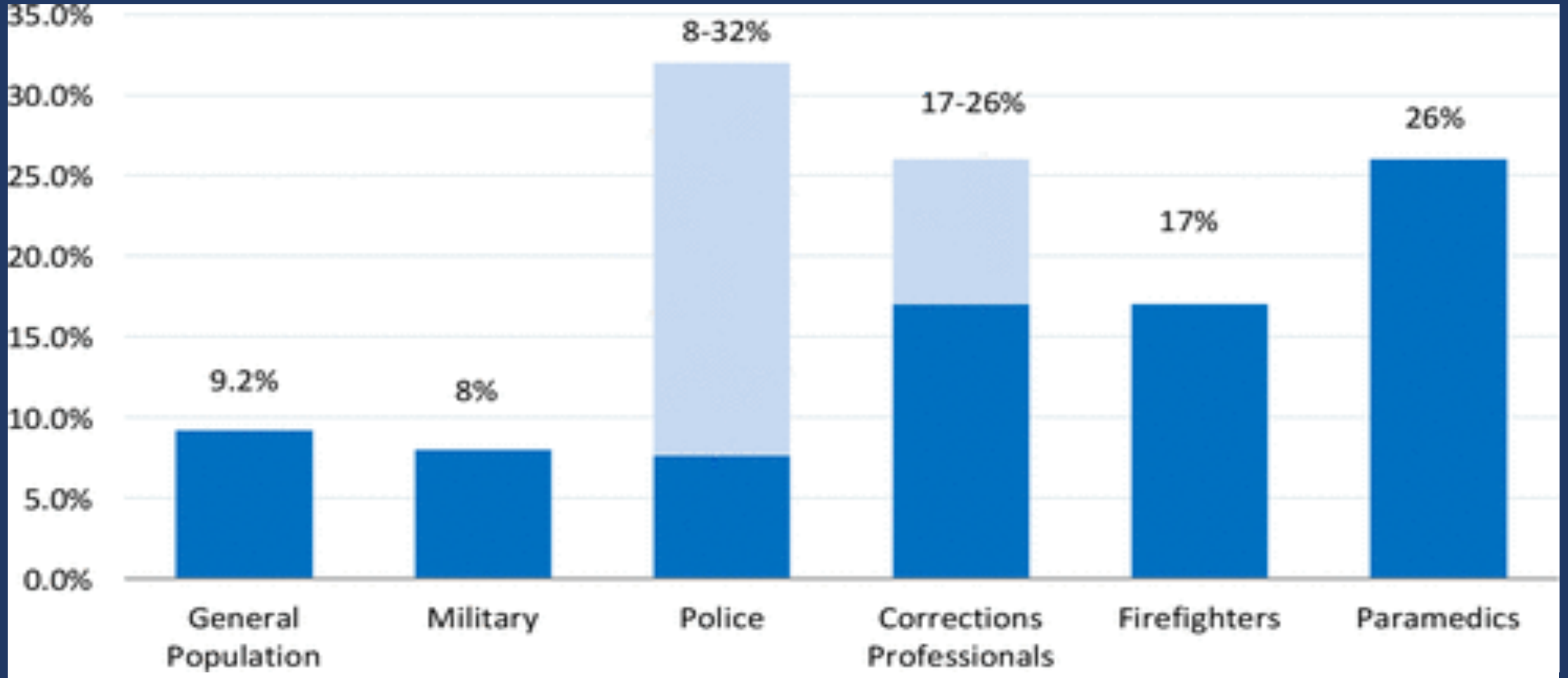
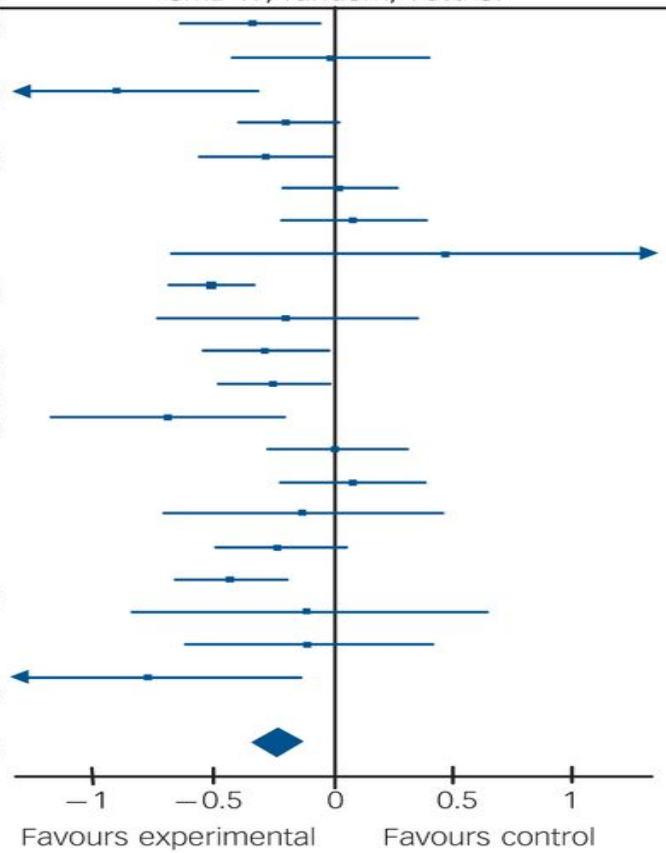


FIGURE 2 Lifetime PTSD Prevalence Rates: Specified Canadian Populations.
Sources: Van Ameringen, Mancini, Paterson et al. (2008); Boulos & Zamorski (2013); Marchand, Boyer, Martin et al. (2010); Asmundson & Stapleton (2008); Rosine (1992); Stadnyk (2004); Corneil, Beaton, Murphy et al. (1999); Regehr, Goldberg & Hughes (2002).

Meta-analysis of selective serotonin reuptake inhibitors v. placebo (SMD, standardised mean difference).

Study or subgroup	Experimental Mean	s.d.	Total	Control Mean	s.d.	Total	Weight	SMD IV, random, 95% CI
Brady (2000)[38]	−33	28.1	94	−23.2	28.7	93	5.8%	−0.34 (−0.63, −0.05)
Brady (2005)[61]	32.56	15.69	49	32.7	28.75	45	4.1%	−0.01 (−0.41, 0.40)
Connor (1999)[40]	10.1	9.8	25	20.5	12.6	22	2.4%	−0.91 (−1.52, −0.31)
Davidson[A]	−39.4	27.12	173	−34.17	28.42	179	7.3%	−0.19 (−0.40, 0.02)
Davidson (2001)[42]	−33	23.76	100	−26.2	23.9	108	6.1%	−0.28 (−0.56, −0.01)
Eli Lilly[B]	−10.42	7.5	323	−10.59	10.21	88	6.8%	0.02 (−0.21, 0.26)
Friedman (2007)[21]	−13.1	27.5	86	−15.4	28.07	83	5.6%	0.08 (−0.22, 0.38)
Hertzberg (2000)[47]	47	8	6	42	11	6	0.8%	0.48 (−0.68, 1.64)
Marshall (2001)[50]	−38.75	27.2	375	−25.3	25.8	188	8.0%	−0.50 (−0.68, −0.32)
Marshall (2004)[64]	55.6	33.4	25	62.8	40.8	27	2.8%	−0.19 (−0.73, 0.36)
Martenyi (2002)[51]	−34.6	28.1	226	26.8	26.1	75	6.3%	−0.28 (−0.54, −0.02)
Martenyi (2007)[23]	−42.85	25.5	323	−36.6	25.7	88	6.8%	−0.24 (−0.48, −0.01)
Panahi (2011)[26]	−22.7	7.3	35	−17.5	7.5	35	3.3%	−0.69 (−1.18, −0.21)
Pfizer 588[C]	−27.4	27.12	94	−27.9	28.42	94	5.9%	0.02 (−0.27, 0.30)
Pfizer 589[D]	−13.1	27.12	84	−15.4	28.42	82	5.6%	0.08 (−0.22, 0.39)
Shaleve (2011)[27]	−31.12	29.63	23	−27.8	20.13	23	2.5%	−0.13 (−0.71, 0.45)
SKB627[E]	−36.5	26.1	109	−30.8	25.37	103	6.2%	−0.22 (−0.49, 0.05)
Tucker (2001)[53]	−35.5	24.58	151	−24.7	24.98	156	7.0%	−0.43 (−0.66, −0.21)
Tucker (2003)[68]	−41.82	29.09	23	−38.7	29.07	10	1.7%	−0.10 (−0.85, 0.64)
Van der Kolk (2007)[70]	−33.23	22.11	30	−30.95	22.6	29	3.0%	−0.10 (−0.61, 0.41)
Zohar (2002)[54]	−18.7	6.7	23	−13.5	6.6	19	2.2%	−0.77 (−1.40, −0.14)
Total (95% CI)			2377			1553	100.0%	−0.23 (−0.33, −0.12)

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 42.90$, d.f. = 20 ($P = 0.002$); $I^2 = 53\%$
Test for overall effect: $Z = 4.23$ ($P < 0.0001$)



Mathew Hoskins et al. BJP 2015;206:93-100

THE BRITISH JOURNAL OF PSYCHIATRY

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Evidence Based Use of medication in PTSD

- Only SSRIs have the highest level evidence
  - Benefit is variable and modest in size
  - Only first line treatment in certain circumstances
- Other Antidepressants may be helpful
- Benzodiazepenes are for short term use wherever possible
- Atypical Antipsychotics may be useful but with a difficult risk benefit equation

NHMRC Guideline Recommendations: Adults

- Trauma focussed CBT or EMDR is the treatment of choice for PTSD:
  - Trauma focused CBT included
    - In vivo and imaginal exposure
    - Cognitive therapy or cognitive processing therapy

- Medication should not be used as routine 1st line in preference to TF psychological treatment

- Where prescribed:
  - SSRIs
  - Other newer antidepressants, tricyclics, phenelzine

Outcomes of Trauma Focussed Therapy

Clinical Bottom Line

- • Posttraumatic stress disorder (PTSD) is a disabling psychiatric condition common among military personnel and veterans
- • A range of psychotherapies are available, but military-PTSD is complex and difficult to treat
- • The available evidence supports the use of structured trauma-focused or non–trauma-focused approaches
- • Although trauma-focused and non–trauma-focused interventions often improve symptoms, many patients continue to meet criteria for PTSD after treatment
- • There is an urgent need for innovative treatment strategies, whether trauma-focused or non–trauma-focused

Steenkamp et al JAMA 2015

Pharmacotherapy and prevention

- Covers the use of pharmacological agents post trauma to prevent development of symptoms
- Limited high level evidence
- ACPMH Guidelines (ACPMH,2013)
  - Should not be used for all those exposed as a preventative intervention

Pharmacotherapy and Prevention

- Pitman et al (Biol. Psychiatry 2002)
  - Propranolol (N= 18) V Placebo (23)
- Stein et al (J. Traumatic Stress 2007)
  - Propranolol (n=17) V Gabapentin(14) V Placebo (17)
  - No impact on severity of PTSD or depressive Symptoms
- Gelpin et al, (J. Clin. Psychiatry,1996)
  - Treatment with Clonazepam/Alprazolam (N= 10) V Placebo (N= 13)
  - No impact of treatment on anxiety or PTSD symptom scores
- Schelling et al (Biol. Psychiatry,2004)
  - Variable dose hydrocortisone V Placebo (N=91)
  - Significant reduction in chronic stress, but not PTSD symptoms in Steroid treated group ($p<.05$)

Conclusion

- PTSD is a common, complex and disabling disorder
- PTSD is particularly common in certain subgroups
- PTSD is a cause of high personal and economic burden
- Currently only Level 1 evidence for SSRIs
  - Effect size small-medium
- Most guidelines recommend psychotherapy as first line treatment but not always appropriate
- Marked unmet need

THANK YOU