UNIVERSITY of OTAGO

SAPERE AUDE

Te Whare Wānanga o Otāgo

Treating alcohol-related depression

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Overview of talk

- Epidemiology and etiology of alcohol-related comorbidity
- Alcohol-related depression in clinical samples
- Evidence
  - Systematic review and meta-analysis
  - The TEAM study

Table 13: Leading causes of burden of disease (DALYs), countries grouped by income, 2004

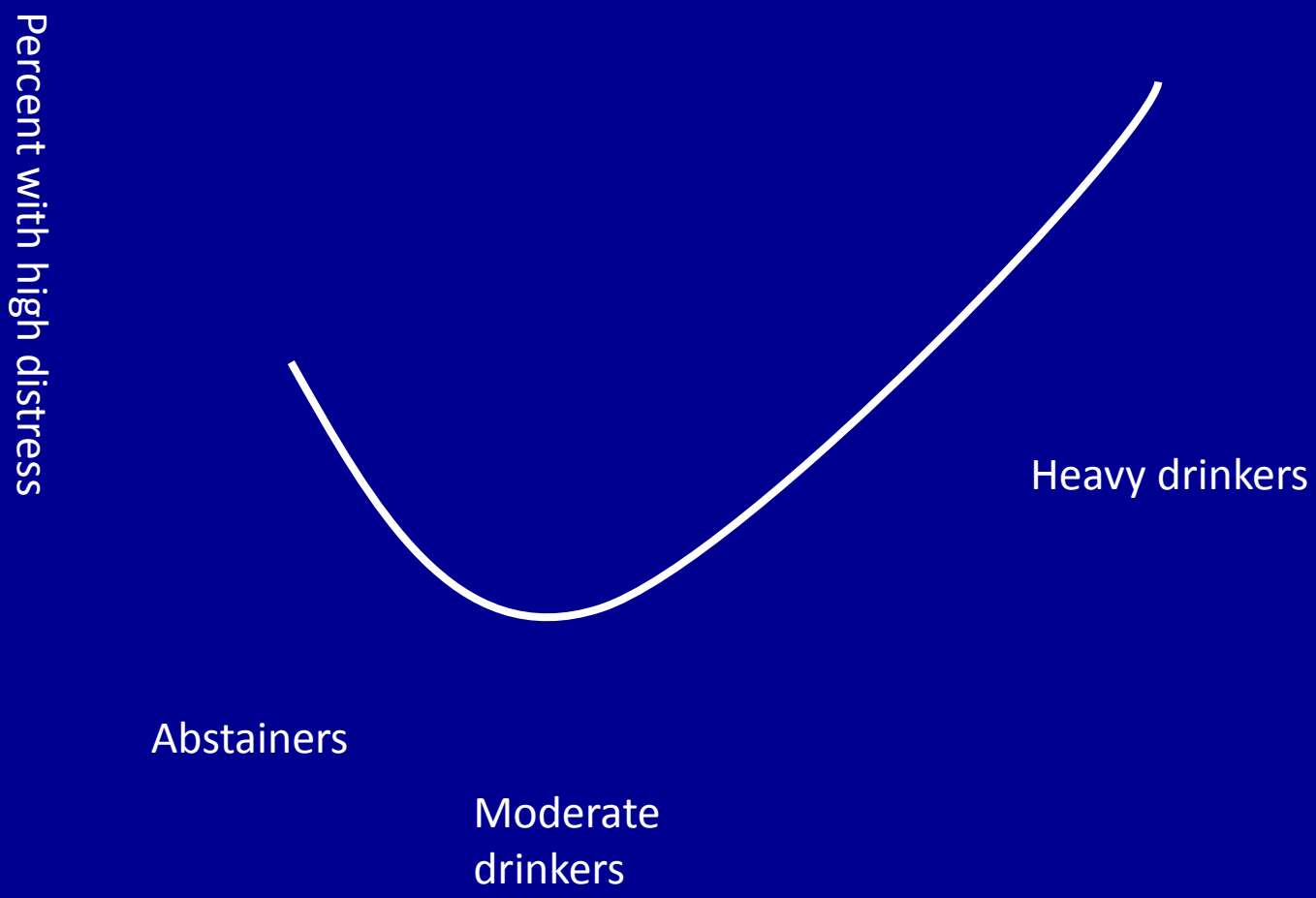
	High-income countries		
1	Unipolar depressive disorders	10.0	8.2
2	Ischaemic heart disease	7.7	6.3
3	Cerebrovascular disease	4.8	3.9
4	Alzheimer and other dementias	4.4	3.6
5	Alcohol use disorders	4.2	3.4
6	Hearing loss, adult onset	4.2	3.4
7	COPD	3.7	3.0
8	Diabetes mellitus	3.6	3.0
9	Trachea, bronchus, lung cancers	3.6	3.0
10	Road traffic accidents	3.1	2.6

Scott, KM et al 2006. Mental disorder comorbidity in Te Rau Hinengaro (NZ Mental Health Survey)

Table 3. Bivariate associations (odds ratios) of DSM-IV 12 month mental disorders,† with hierarchy

	Panic disorder	Agoraphobia	Specific phobia	Social phobia	GAD	PTSD	OCD	Major depression	Dysthymia	Bipolar disorders
Panic disorder	–									
Agoraphobia	–	–								
Specific phobia	7.27**	10.10**	–							
Social phobia	9.59**	28.05**	6.22**	–						
GAD	7.67**	9.70**	3.14**	6.39**	–					
PTSD	7.68**	8.27**	5.66**	5.05**	1.78	–				
OCD	13.64**	6.97**	4.53**	5.41**	12.23**	9.48**	–			
Major depression	8.37**	5.44**	3.50**	4.86**	8.34**	6.11**	4.94**	–		
Dysthymia	12.19**	4.08**	4.74**	8.34**	4.13**	8.00**	12.41**	–	–	
Bipolar disorders	9.36**	9.86**	4.17**	6.27**	5.46**	7.73**	12.37**	–	–	–
Alcohol abuse	5.41**	3.64**	2.14**	3.51**	1.66	2.62**	10.16**	2.74**	3.45**	7.98**
Alcohol dependence	8.79**	5.11**	3.88**	5.69**	2.83*	4.03**	10.96**	3.54**	5.02**	11.85**
Drug abuse	10.02**	3.14*	3.22**	6.03**	4.5**	5.51**	8.52**	4.17**	4.99**	9.06**
Drug dependence	10.38**	4.62*	4.82**	8.56**	6.80**	7.51**	2.67	8.04**	15.62**	10.61**

Alcohol and psychological distress: the J-shaped curve



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A comparison of alcohol measures as predictors of psychological distress in the New Zealand population

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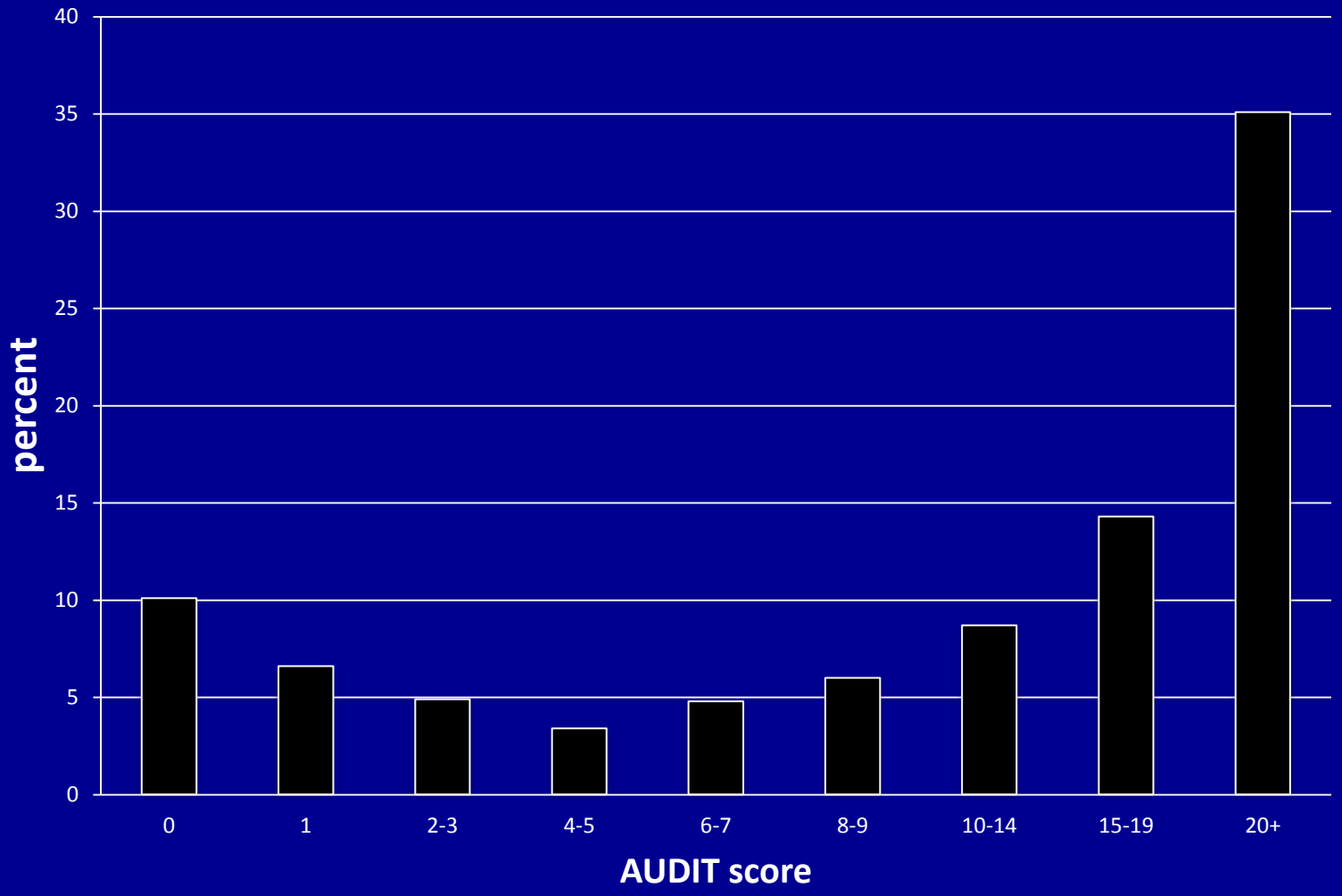
Percent with high psychological distress, by AUDIT score category



Source: NZ Health Survey 06/07

Adamson et al, 2006. Co-existing disorders in a New Zealand Outpatient Alcohol and other Drug Clinical Population

Table 2. Mood, anxiety, eating, conduct and antisocial personality disorder in an alcohol and other drug outpatient sample (n = 105)

Diagnosis	Current %	Current 95% CI
Major depressive episode, single episode	10	4–16
Major depressive episode, recurrent	24	15–32
Bipolar I disorder	11	5–18
Dysthymic disorder	9	4–15
Substance induced mood disorder	8	3–14
Obsessive– compulsive disorder	20	12–28
Posttraumatic stress disorder	31	22–40
Panic disorder without agoraphobia	4	0–8
Panic disorder with agoraphobia	13	7–20
Agoraphobia without history of panic disorder	8	3–13
Social phobia	31	22–40
Generalized anxiety disorder	1	0–4
Specific phobia	22	14–30
Anorexia nervosa	0	–
Bulimia nervosa	0	–
Any mood disorder	53	44–63
Any anxiety disorder	65	55–74
Any mood/anxiety/eating disorder	74	66–83
Conduct disorder	0	–
Antisocial personality disorder	27	19–36

Correlates of depressive comorbidity in substance use disorder samples

- ⇧ service utilisation
- ⇧ relapse
- ⇧ disability
- ⇧ suicide risk

Plausible mechanisms of association

- Common underlying cause, eg genes & early environment
- Alcohol causes mental illness, either via direct pharmacological effect or via life problems
- Mental illness promotes drinking, eg as a maladaptive coping strategy
- Bidirectional causation

Does alcohol causes depression?

- Probably, but demonstrating this conclusively is ethically difficult
- Experimental studies in late 1960s showed heavy drinking increased levels of anxiety and depression
- More circumstantial evidence from multiple other lines of research, eg cohort studies (not discussed today)

Does depression lead to drinking?

- Sometimes, but usually not
- Some evidence for motivational model of alcohol use (people drink to enhance positive affect or reduce negative affect)
- However, most patients with major depression if anything *reduce* rather than *increase* their alcohol use

Summary

- The causal relationship between alcohol and depression…
  - is complex
  - varies between patients
  - probably varies within patients over time
  - is difficult to be certain about for any individual patient

Independent vs substance-induced depression

- Independent= depression present before onset of heavy drinking, or present during abstinence
- Otherwise= substance induced
- This typology widely believed to be valid and useful (eg Schuckit 2007; Pettinati 2013)

Research questions:

- How much does depression improve during treatment?
- What is the effect of antidepressants?
- What predicts depression outcomes?
- Does it matter if depression is categorised as independent or substance-induced?

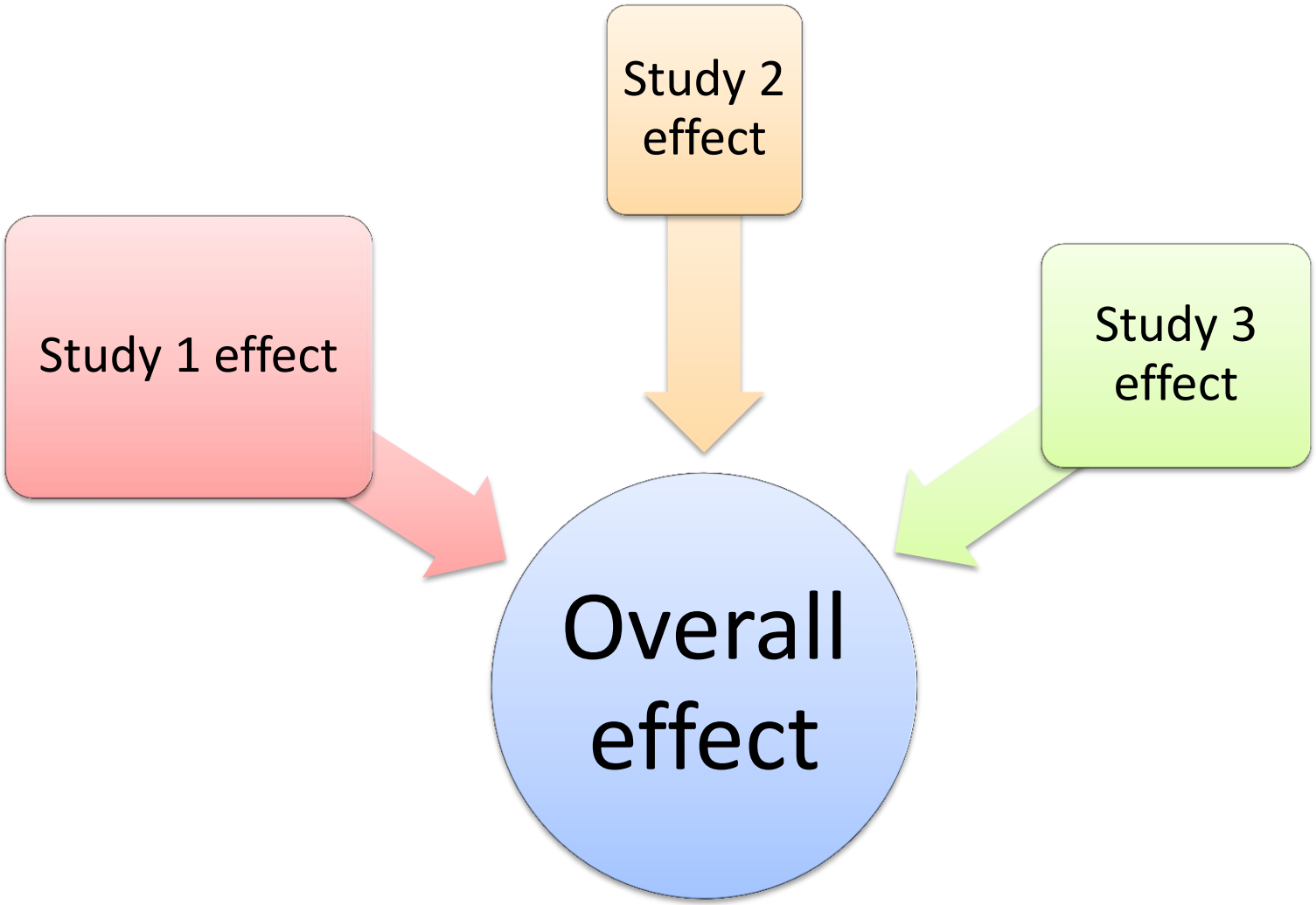
Methods

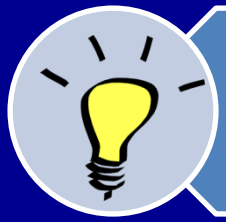
- 1. Systematic review and meta-analysis: J Foulds, S Adamson, R Mulder, J Williman, J Boden

- 2. Treatment Evaluation of Alcohol and Mood (TEAM) study:

S Adamson, D Sellman, J Foulds, L Nixon, G Cape et al

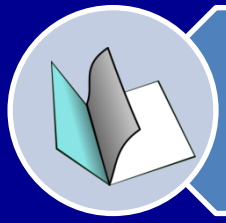
Meta-analysis





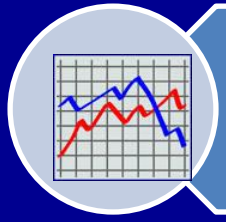
Define the research question and write a protocol

Conduct literature search (preferably 2 independent authors)



Extract data from studies

Analyse data using meta-analysis model



Summarise and interpret data

Inclusion criteria

Studies were chosen according to the following criteria:

1. Studies with longitudinal data on alcohol use and depression over 8+ weeks in treatment-seeking populations
2. Subjects had a currently active alcohol use disorder
3. Mean baseline depression score ≥ 10 on the 17-item Hamilton Depression Rating Scale (or equivalent)

Search strategy

- MEDLINE, Embase and Cochrane databases plus reference lists from review articles in the field and the reference lists of studies in the final sample
- Search items were alcohol drinking; alcohol-induced disorder; alcohol-related disorder; alcoholics; alcoholism AND depression; antidepressive agents.
- English-language publications on subjects aged 18+ from 1980 onwards were considered.

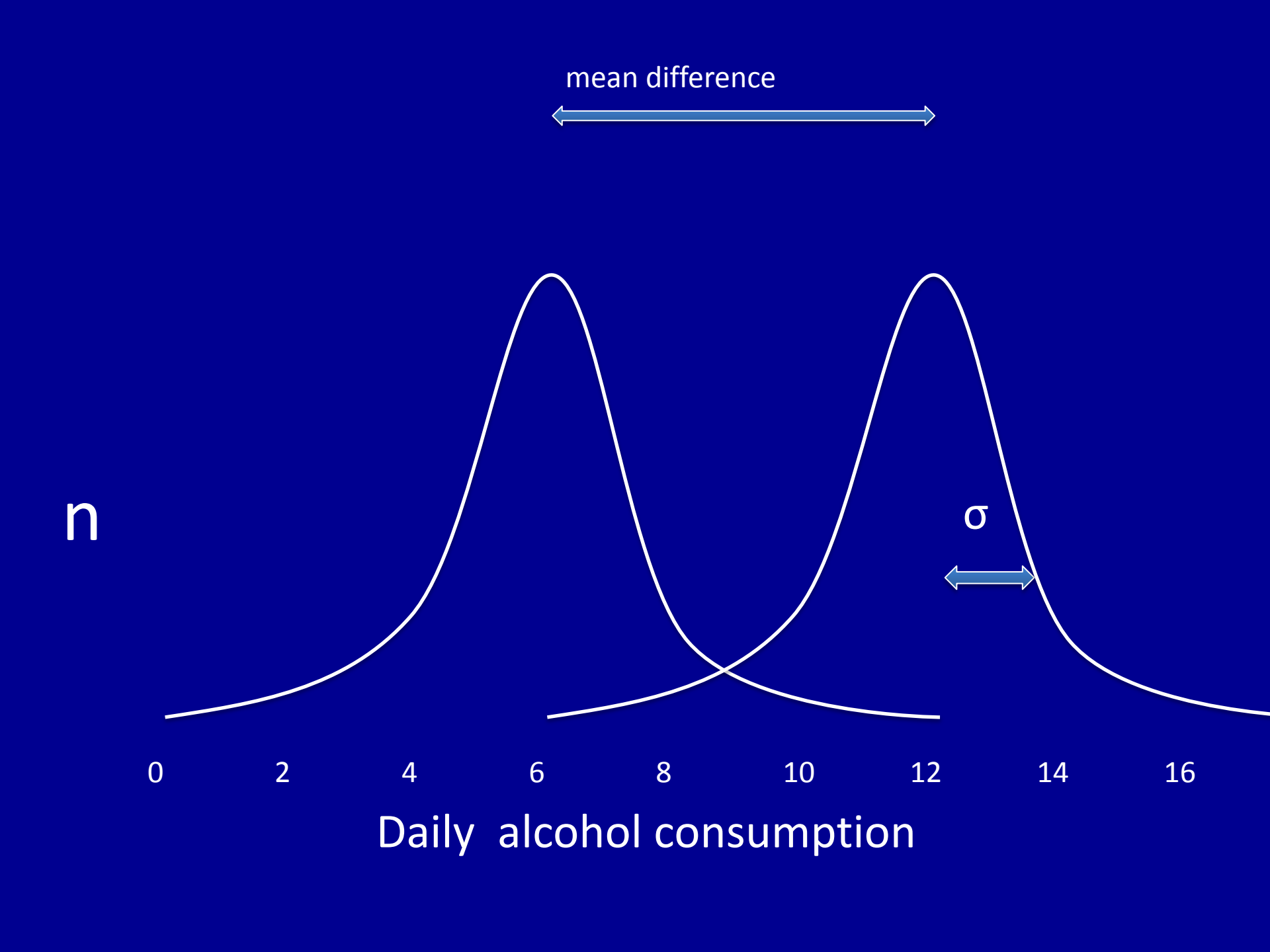
Findings

- 22 studies identified, 11 included in meta-analysis
- Most studies were in mild-moderately depressed subjects
- Most studies were pharmacotherapy trials of antidepressants

Understanding effect sizes

- Question is **not** *is this difference statistically significant (p value)*
- Rather, *how large is the group difference*
- Effect size is a critically important concept when interpreting literature on treatments

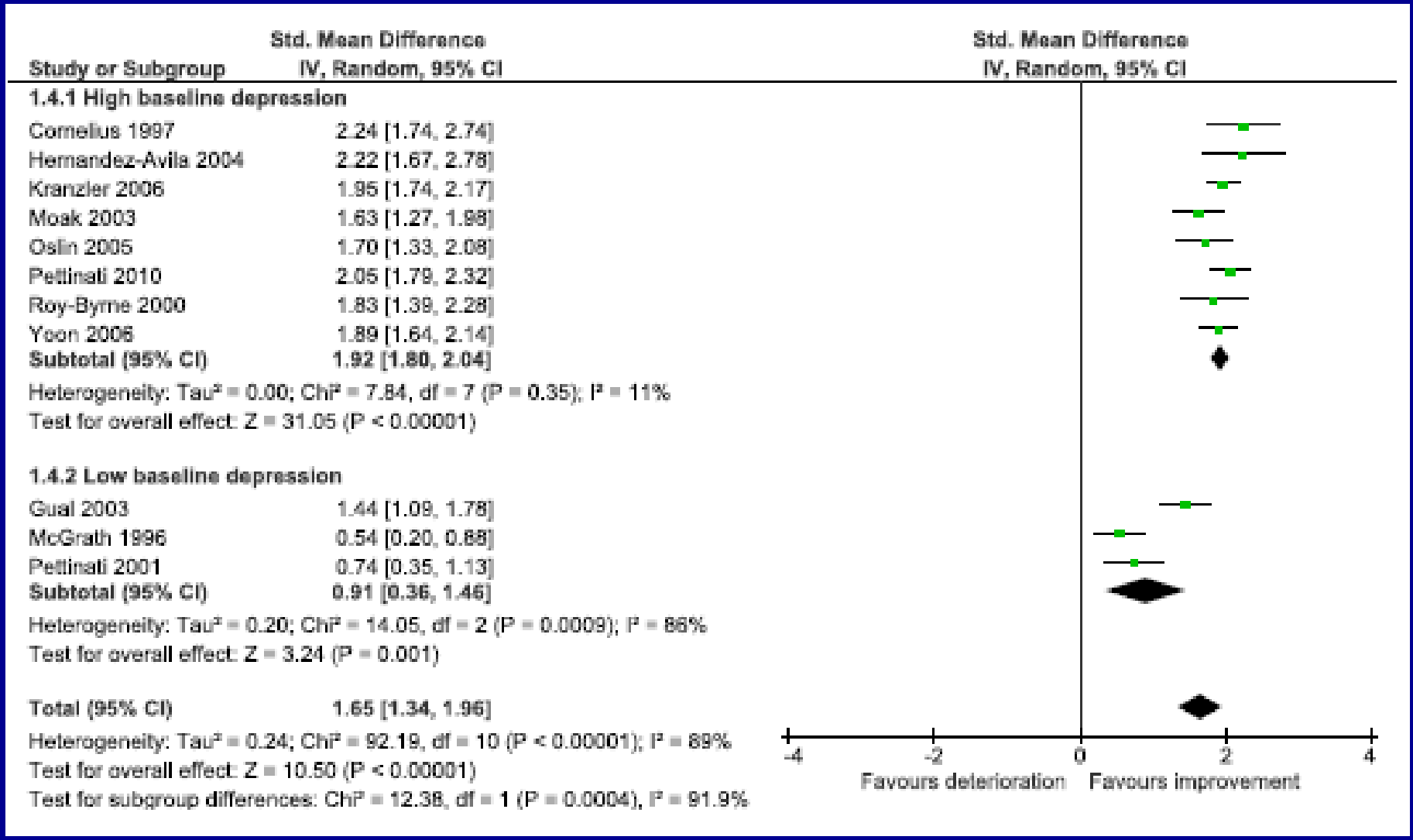
- Many difference types of effect sizes (r value; standardised mean difference; odds ratio etc)


mean difference
n
σ
0
2
4
6
8
10
12
14
16
Daily alcohol consumption

Standardised mean difference

$$d = \frac{\bar{X}_2 - \bar{X}_1}{\sigma}$$

Change in depression with treatment



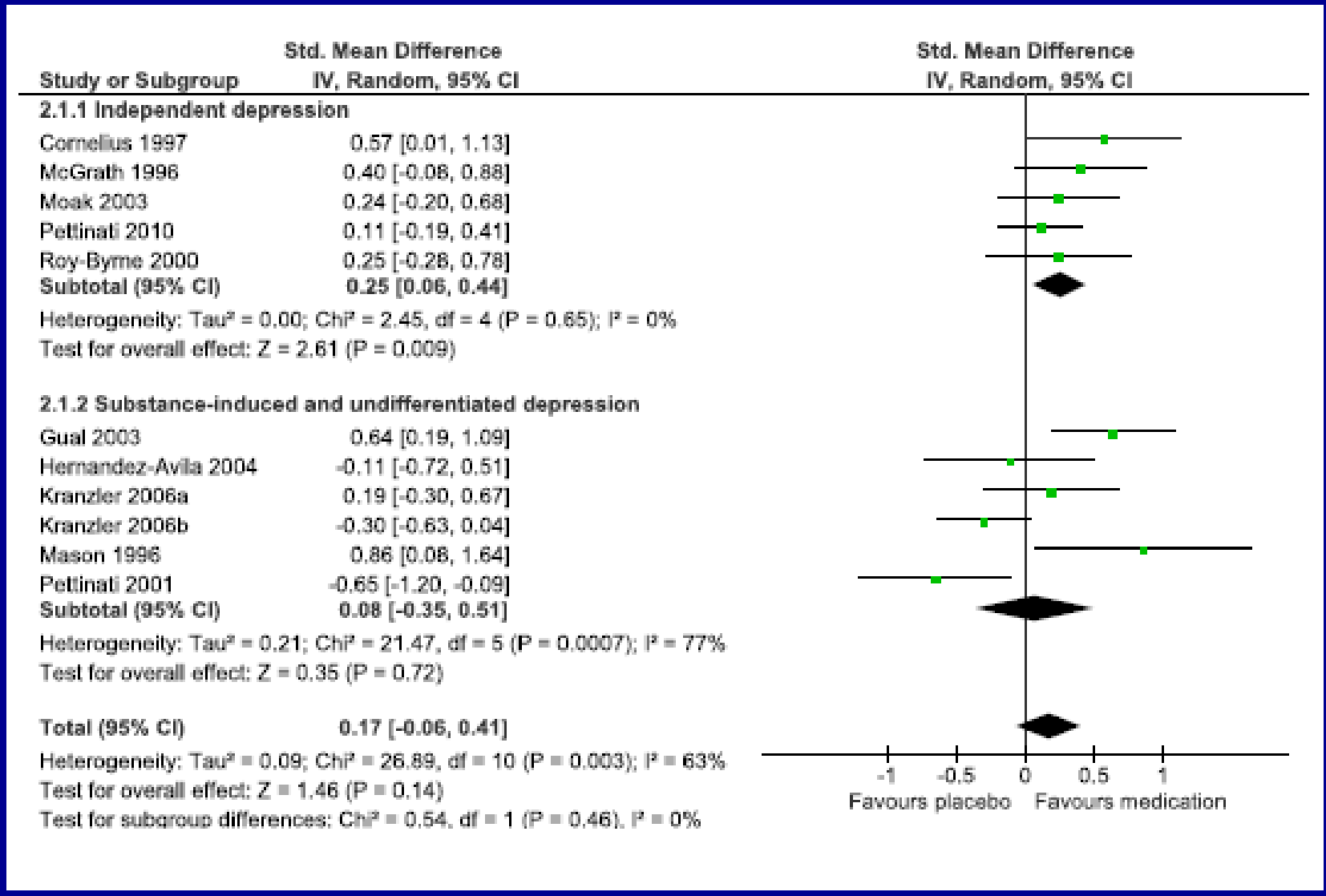
What is an effect size of 2?

- Depression score reduced by 2 standard deviations on average
- Equates to a 10 to 15 point reduction in Hamilton score
- A large effect
- ie moderate depression -> mild depressive symptoms

Independent vs substance-induced

- similar improvement in depression regardless of whether independent, substance-induced or undifferentiated depression
- no evidence reduced drinking benefits substance-induced depression more (probably benefits all patients)
- **however** the quality of evidence on substance-induced depression was low

Antidepressant effect



Meta-analysis summary

- Large early improvement in depression regardless of depression type and treatment provided
- Improvement reaches a plateau within 6-12 weeks
- Significant minority of patients remains depressed
- Antidepressants at best have very modest effect
- Evidence for antidepressants strongest in independent depression
- Reduced drinking probably helps depression

The TEAM study

- Multi-site RCT conducted in NZ (Prof Doug Sellman, Assoc Prof Simon Adamson principal investigators)
- n=138
- Naltrexone + citalopram / placebo
- 12 week active treatment phase + naturalistic follow up at 24 at 64 weeks
- All subjects received manualised clinical case management
- Subjects not abstinent at baseline (in keeping with standard outpatient practice)

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A Randomized Trial of Combined Citalopram and Naltrexone for Nonabstinent Outpatients With Co-Occurring Alcohol Dependence and Major Depression

Simon J. Adamson, PhD, J. Douglas Sellman, PhD,* James A. Foulds, MB ChB,* Christopher M.A. Frampton, PhD,* Daryle Deering, PhD,* Alistair Dunn, FAChAM,† John Berks, FRANZCP,‡ Lee Nixon, PhD,§ and Gavin Cape, FRANZCP‖*

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research Report

Depression outcome in alcohol dependent patients: An evaluation of the role of independent and substance-induced depression and other predictors

James A. Foulds [a,*], J. Douglas Sellman [a], Simon J. Adamson [a], Joseph M. Boden [b], Roger T. Mulder [a], Peter R. Joyce [a]

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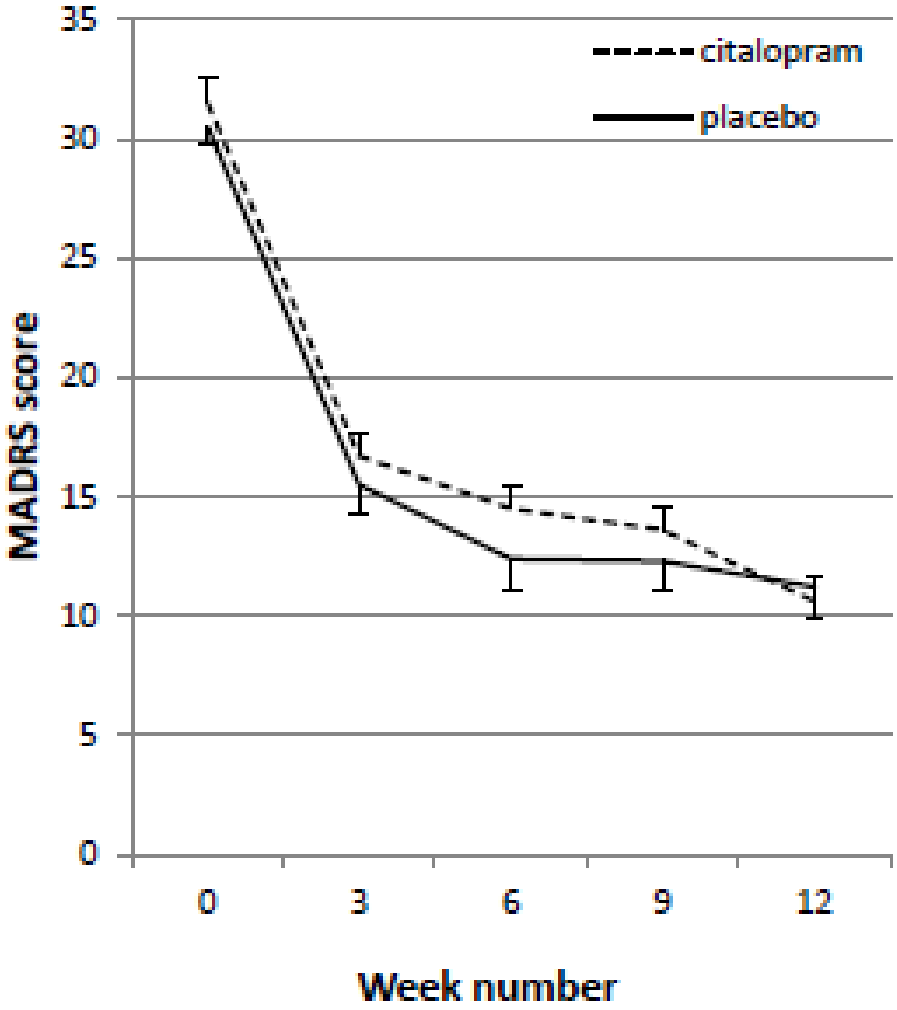
Baseline sample characteristics

	Total Sample	Citalopram n=73	Placebo n=65	p
Age	43.6 (9.1)	44.6 (8.6)	42.4 (9.5)	**.148**
Female	59.4%	60.3%	58.5%	**.829**
NZ Maori	17.4%	15.1%	20.0%	**.446**
Employed	55.1%	53.4%	56.9%	**.680**
Antidepressants	76.1%	80.8%	70.8%	**.167**
Independent depression	76.1%	69.9%	83.1%	**.069**
Major Depressive Disorder, onset age	24.3 (11.4)	26.3 (12.4)	22.2 (9.9)	**.035**
MADRS	31.0 (5.8)	31.3 (5.6)	30.6 (6.0)	**.434**
Percent Days Abstinent (PDA)	25.8 (27.4)	25.5 (28.4)	26.1 (26.4)	**.906**
Percent Days Heavy Drinking (PDH)	58.9 (33.6)	60.7 (34.9)	56.8 (32.2)	**.505**
Drinks Per Drinking Day (DDD)	14.3 (8.0)	14.3 (7.4)	14.4 (8.6)	**.909**

Effect of citalopram



Effect of depression type

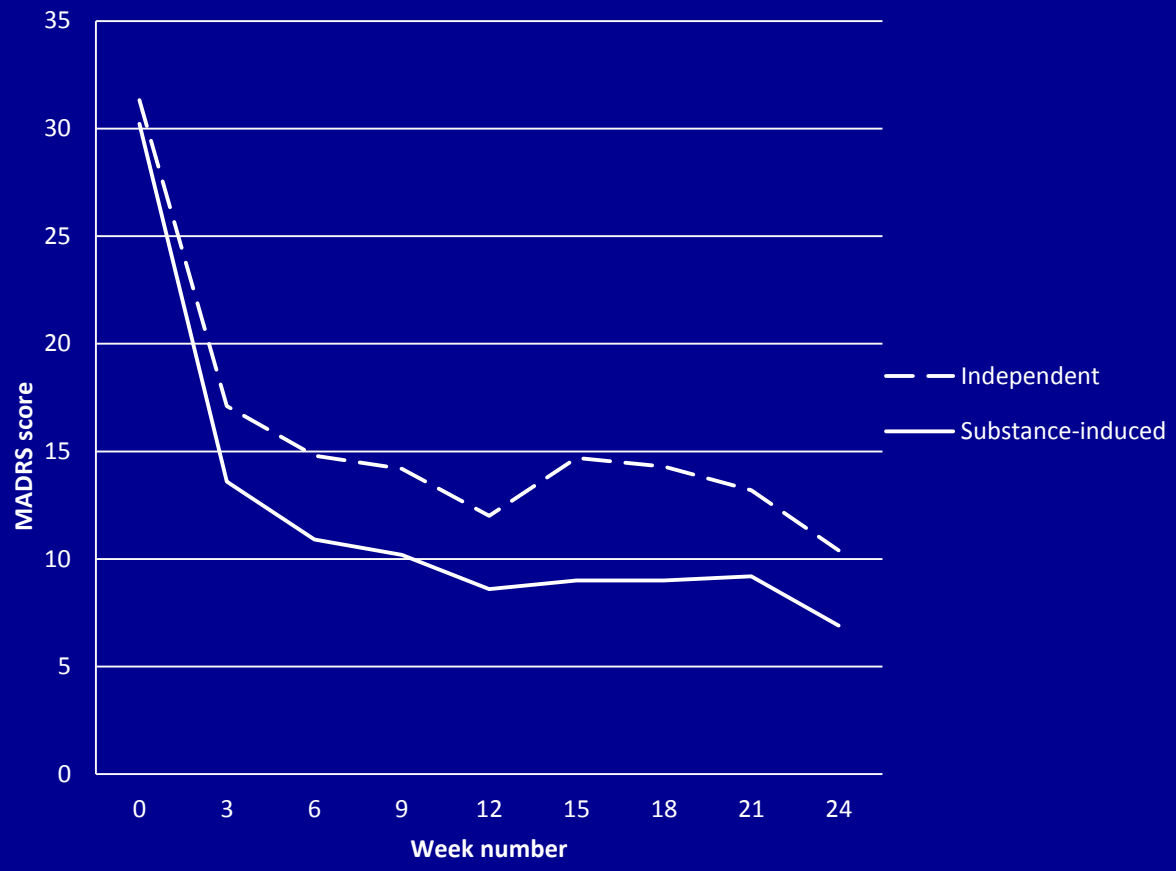
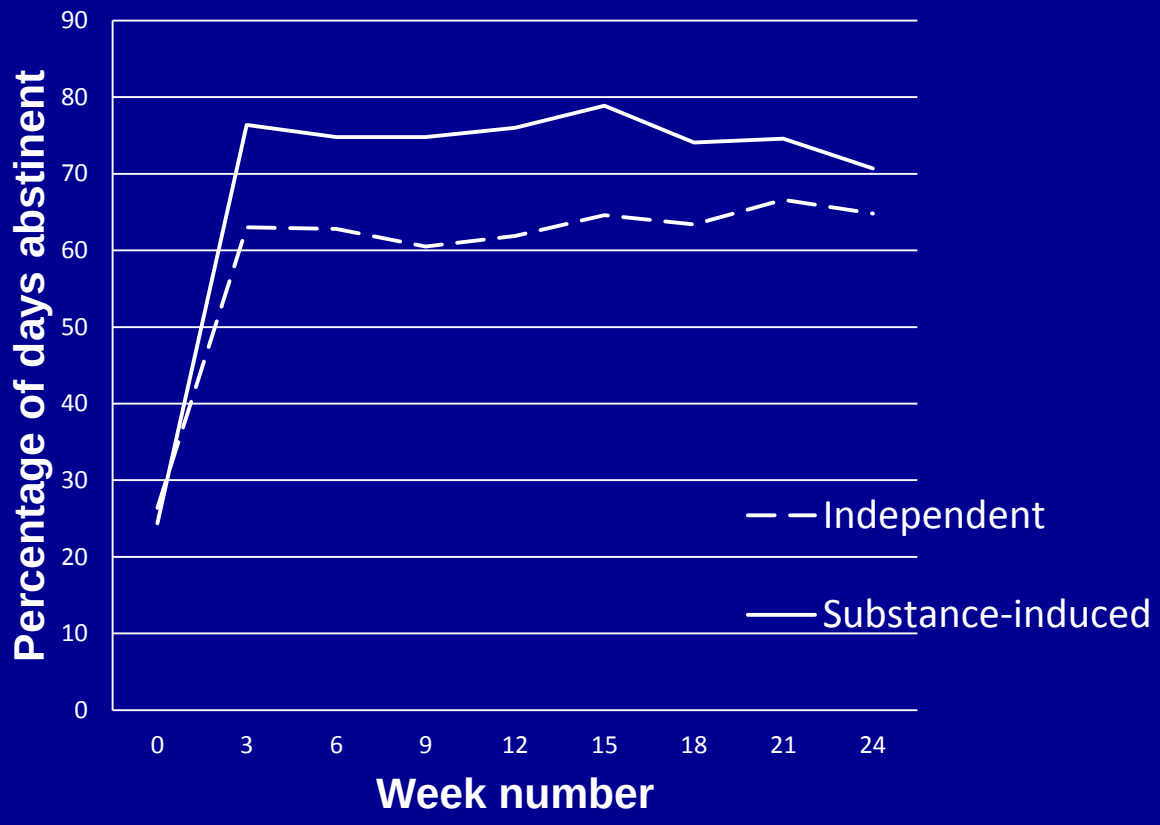


Figure 1:MADRS score from baseline to week 24, for subjects with independent and substance-induced depression; p value=.004 for the overall difference between groups in repeated measures analysis. Estimates of MADRS score at timepoints from week 3 to week 24 are least squares means from linear mixed models including time as a categorical predictor. Standardised mean difference 0.68 for group difference across all timepoints (excluding baseline) and 0.54 for group difference at week 24.

Change in percent days abstinent

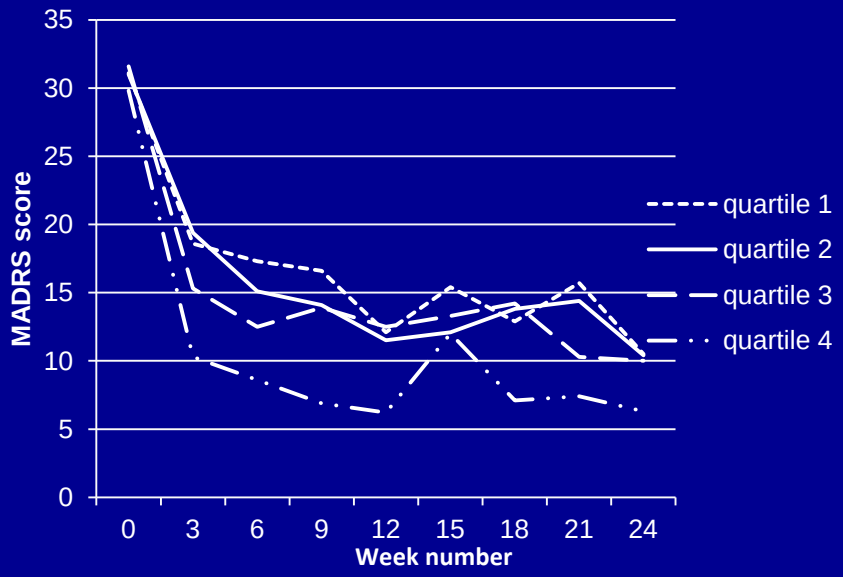


Relationship between change in depression and change in drinking

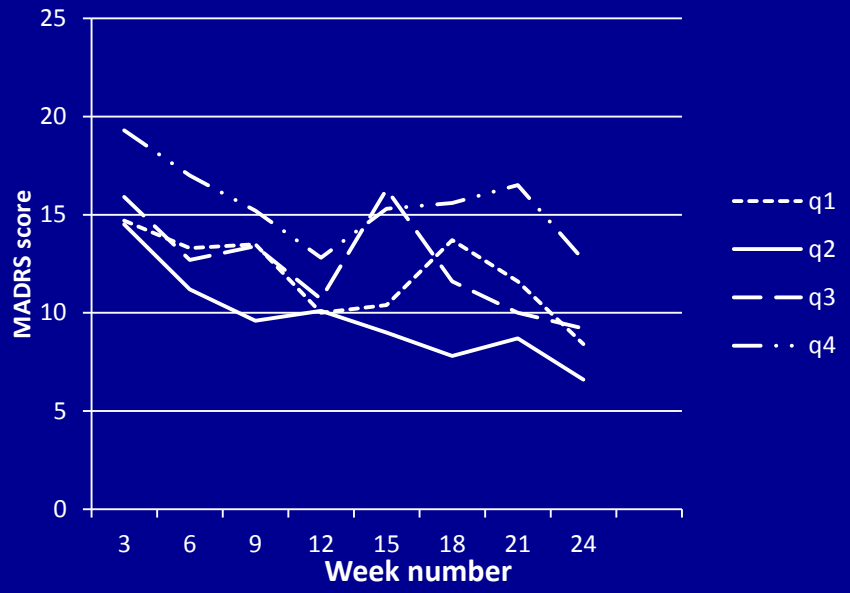
Drinking outcome	n	% of sample	Percent improvement in MADRS from baseline to 24 weeks % (SE)
No improvement in percent days abstinent	22	15.9	41.0 (5.8)
Increased days abstinent; still drinking >50% of days	27	19.6	62.0 (4.4)
Increased days abstinent, drinking <50% of days	59	42.8	77.6 (5.0)
Total abstinence last 3 weeks of study	30	21.7	73.3 (3.9)
			ANOVA for group differences: $F=9.4$, $p<0.001$

Personality and depression outcome

Self-directedness



Harm avoidance



TEAM study summary

- No effect of citalopram in this sample
- Rapid large improvement in depression and drinking
- Subjects who did not increase their percentage of abstinent days had much worse depression outcomes
- Substance-induced depression patients had more change in both drinking and depression
- Personality traits influence depression outcome

Other drug classes

- No evidence naltrexone helps or worsens depression
- Little evidence for other classes of drugs eg lithium

Psychological treatments

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review

Psychological interventions for alcohol misuse among people with co-occurring depression or anxiety disorders: A systematic review

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Overall: limited evidence available overall; however some evidence for CBT and integrated motivational interventions targeting both drinking and mood

Summary

- Antidepressants relatively ineffective in alcohol use disorders
- Standard treatment produce rapid, large improvements in depression
- Probably not very useful to determine whether depression is alcohol-induced
- Reduced drinking associated with better depression outcomes; this may be partly causal
- Specific psychological therapies may be useful but limited evidence
- Personality predicts depression outcome

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  Simon Adamson
  Doug Sellman
  Roger Mulder
  Joe Boden
  Elisabeth Wells

- Thanks to TEAM study participants, research clinicians and Medical Officers