

A pilot randomised controlled trial of varenicline versus oral naltrexone for the treatment of alcohol dependence

Nicholas Lintzeris, Mark Montebello,
Lauren Monds, Consuelo Rivas, David
Allsop, Selena Bartlett & Paul Haber

Mark.Montebello@health.nsw.gov.au

AP SAD Conference Sydney, 2nd November 2016



Health
South Eastern Sydney
Local Health District

Background 1

- Alcohol dependence is the most common substance use disorder in Australia
- Limited number of effective relapse prevention medications (naltrexone, disulfiram, acamprosate) – more are required
- Varenicline (Champix®) is a partial $\alpha 4\beta 2$ nicotinic acetylcholine receptor agonist approved for tobacco cessation

Background 2

- Varenicline for alcohol consumption:
 - At least 3 animal studies found reduced alcohol consumption (Steensland et al 2007, Ericson et al 2009, Wouda et al 2011)
 - Two DBRCTs found reduced heavy alcohol consumption in alcohol dependent individuals (Mitchell et al Psychopharmacology 2012, Litten et al Journal of Addiction Medicine 2013)
- There are no studies comparing varenicline to an active control group

Aims

- To conduct a pilot study examining the feasibility of conducting a safety and efficacy RCT of varenicline (experimental condition) compared to oral naltrexone (active control) for the outpatient treatment of alcohol dependence



Method 1

- Conducted at The Langton Centre, SESLHD
- Design: double-blinded, parallel-group randomised active-controlled trial over an 8-week medication period
- Treatment-seeking alcohol-dependent patients were allocated into one of the two groups using a 1:1 random allocation:

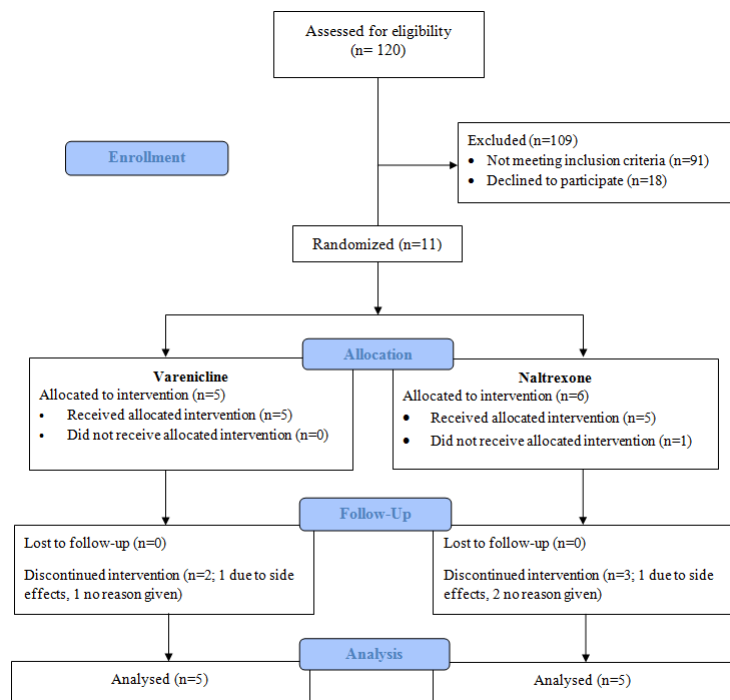
Medication	Week 1 Day 1-3	Week 1 Days 4-7	Weeks 2-8
Varenicline	0.5mg morning only	0.5mg BD (morning and evening)	1mg BD (morning and evening)
Naltrexone	25mg daily	50mg morning, placebo evening	50mg morning, placebo evening

Method 2

- Participant eligibility:
 - Age 18-65
 - Proficient in English
 - ICD 10 criteria for alcohol dependence
 - Seeking to stop or reduce alcohol intake
 - No severe active comorbidity
 - Stable >1 month on psychotropic medication
 - No contraindications to naltrexone & varenicline
 - No relapse prevention treatment in <2 months

Method 3

- Primary outcome measures:
 - Alcohol consumption (TLFB, AUDIT, Penn Craving Scale)
 - Side effects & Adverse Events
- Secondary measures:
 - Other substance use (ATOP, Fagerstrom)
 - Physical & mental health (DASS21; PHQ-15; SF-36; Insomnia Severity)
 - Patient satisfaction
- Procedure: Baseline research assessment prior to or during Week 1, and completed follow-up research assessments Week 4 and 8 (\$40/research assessment)



Results – Baseline Demographics, Drinking Days, Tobacco Use

	Varenicline N=5	Naltrexone N=5	Total N=10
Age Mean (SD)	43.60 (9.37)	46.40 (9.50)	45.00 (9.02)
Gender (% male)	60%	80%	70%
Alcohol Use			
Days Used in Last 28 Days Mean (SD)	9.40 (9.61)	13.40 (8.32)	11.40 (8.70)
Days Used in Last 7 Days Mean (SD)	2.80 (3.83)	2.80 (3.83)	2.80 (3.60)
Heavy Drinking Days Mean (SD)	9.00 (9.75)	12.60 (8.68)	10.80 (8.90)
Past Detox Episodes Mean (SD)	1.80 (1.30)	4.20 (6.14)	3.00 (4.40)
AUDIT scores Mean (SD)	23.25 (4.03)	28.20 (5.45)	26.00 (5.27)
Tobacco Use			
Cigarettes Smoked Last 28 Days Mean (SD)	104.5 (0)	616.67 (217.33)	488.63 (311.56)
Fagerstrom score Mean (SD)	0	6.50 (3.54)	4.33 (4.51)

Results – Drinking Days

	Varenicline Baseline N=5	Naltrexone Baseline N=5	Varenicline Follow Up 2 N=4	Naltrexone Follow Up 2 N=2
Abstinence Rates (%)	0	0	3/4 (75%)	1/2 (50%)
Abstinent assuming relapse in drop outs (%)	0	0	3/5 (60%)	1/5 (20%)

Results – AUDIT, Penn Craving Scale

	Varenicline Baseline N=5	Naltrexone Baseline N=5	Varenicline Follow Up 2 N=4	Naltrexone Follow Up 2 N=2
AUDIT mean (SD)	23.25 (4.03)	28.20 (5.45)	22.75 (6.40)	12.75 (14.77)
Penn Craving mean (SD)	20.75 (5.91)	26.00 (4.24)	8.75 (6.90)	13.00 (9.90)

Results – ATOP, DASS

	Varenicline Baseline N=5	Naltrexone Baseline N=5	Varenicline Follow Up 2 N=4	Naltrexone Follow Up 2 N=2
ATOP Psych mean (SD)	4.8 (1.9)	5.2 (1.6)	8.0 (1.6)	6.5 (2.1)
ATOP Physical mean (SD)	6.2 (1.9)	4.6 (2.7)	6.8 (3.0)	7.5 (0.7)
ATOP QoL mean (SD)	4.6 (1.7)	5.2 (2.6)	8.0 (1.8)	7.0 (1.4)

Results – Side Effects

Side effect	Follow up 1 (Week 4)		Follow up 2 (Week 8)	
	Naltrexone	Varenicline	Naltrexone	Varenicline
Insomnia	0	1 (mild) /3	0	2 (1 mild, 1 severe) /4
Abnormal dreams	1 (mod) /2	1 (severe) /3	1 (mild) /2	2 (1 mod, 1 severe) /4
Nausea	0	2 (1 mild, 1 severe) /3	0	3 (1 mild, 2 severe) /4
Anxiety	1 (mod) /2	1 (mild) /3	1 (mod) /2	3 (2 mild, 1 mod) /4
Depressed mood	1 (mild) /2	2 (mild) /3	0	2 (mild) /4

Results – Other

- The only smoker in varenicline group lost to FU
- One smoker in naltrexone group reduced smoking
- No significant increase in other substance use
- Difficulties with blinding?
 - 3/4 varenicline and 1/2 naltrexone group guessed what they were taking (possibly due to previous exposure to naltrexone?)

Varenicline Case Study 1

- 37 yo, female, married, home duties
- Admitted SSEH for alcohol detox before study
- Medn - fluvoxamine for major depression
- Non smoker
- Baseline alcohol - AUDIT 19, 14 days in 28
- Week 4 alcohol - AUDIT 16, 0 days in 28
- Baseline and follow up Ix - all NAD
- Outcome - remained abstinent, completed trial

Varenicline Case Study 2

- 47 yo, male, separated, self employed
- Langton Centre outpt alcohol detox before study
- Medication - symbicort for asthma
- Smoker 20 cigs/day
- Baseline alcohol - AUDIT 21, 26 days in 28
- Week 8 alcohol - AUDIT 19, 28 days in 28
- Baseline Ix - GGT155, MCV101, others NAD
- Outcome - side effects → refused study medication

Conclusions

- For those who remained in treatment, the number of days of drinking decreased and physical & mental health improved
- The results of this pilot study should inform the design of future large scale efficacy studies including difficulties with recruitment, dropout rate and (possibly) blinding

Thanks ... any questions?

- Staff and participants at The Langton Centre, Drug & Alcohol Service, SESLHD
- NSW MHDAO part funded this project
- Contact:
Mark.Montebello@health.nsw.gov.au



Health
South Eastern Sydney
Local Health District

Additional Slides

Results – Drinking Days (TLFB)

Participant	Condition	Days Drinking Baseline /28	Days Drinking Baseline /7	Days Drinking Follow up 1 /28	Days Drinking Follow up 1 /7	Days Drinking Follow up 2 /28	Days Drinking Follow up 2 /7	Notes
1	Naltrexone	10.00	.00					LTFU
2	Naltrexone	7.00	.00	.00	.00	.00	.00	
3	Varenicline	5.00	.00	.00	.00	.00	.00	
4	Varenicline	2.00	.00	1.00	1.00	.00	.00	
5	Varenicline	9.00	7.00	.00	.00	.00	.00	
6	Naltrexone	28.00	7.00	2.00	.00	1.00	.00	
7	Varenicline	5.00	.00					LTFU
8	Naltrexone	11.00	.00					LTFU
9	Varenicline	26.00	7.00			28.00	7.00	Did not complete follow up 1
10	Naltrexone	11.00	7.00					LTFU

LTFU = lost to follow up

Results – Drinking Days

	Varenicline			Naltrexone			Total		
	Baseline	FU1	FU2	Baseline	FU1	FU2	Baseline	FU1	FU2
Total N	5	3	4	5	2	2	10	5	6
Abstinence rates %	0	2/3 (67%)	3/4 (75%)	0	1/2 (50%)	1/2 (50%)	0	3/5 (60%)	4/6 (67%)
Abstinent assuming relapse in dropouts %	0	2/5 (40%)	3/5 (60%)	0	1/5 (20%)	1/5 (20%)	0	3/10 (30%)	4/10 (40%)
Mean (SD) days drinking/ 28	9.40 (9.61)	1	28	13.4 (8.32)	2	1	11.4 (8.7)	1.5 (0.71)	14.5 (19.09)
Mean (SD) Days Heavy drinking /28	10.25 (10.8)	1 (0)	26 (0)	12.6 (8.7)	0	1(0)	10.08 (8.90)	1 (0)	13.50 (17.6)

Results – Other

	Naltrexone			Varenicline			Total		
	Baseline	FU1	FU2	Baseline	FU1	FU2	Baseline	FU1	FU2
N	5	1-2	2	5	1-3	3-4	10	4-5	5-6
ATOP Psych	5.20 (1.64)	8 (1.4)	6.5 (2.1)	4.8 (1.9)	7.3 (2.5)	8.0 (1.6)	5.00 (1.70)	7.6 (1.9)	7.5 (1.8)
ATOP Physical	4.60 (2.70)	7.5 (0.7)	6.5 (2.1)	6.2 (1.9)	7.7 (2.5)	6.8 (3.0)	5.40 (2.37)	7.6 (1.8)	6.7 (2.5)
ATOP QoL	5.20 (2.59)	8.0 (1.4)	7.0 (1.4)	4.6 (1.7)	7.0 (2.0)	8.0 (1.8)	4.90 (2.08)	7.4 (1.7)	7.7 (1.6)
SF36 PCS	44.66 (7.64)	41.9 (12.4)	47.35 (15.0)	52.8 (11.6)	56.9 (1.1)	51.9 (10.9)	48.74 (10.23)	50.9 (10.3)	50.4 (11.0)
SF36 MCS	33.72 (15.52)	50.8 (11.4)	47.2 (3.0)	27.5 (9.3)	48.7 (12.0)	47.6 (9.9)	30.63 (12.51)	49.6 (10.3)	47.5 (7.8)
PHQ15	9.00 (3.56)	3 (0)	N/A	8.6 (4.2)	4.0 (3.0)	3.0 (0)	8.78 (3.67)	3.8 (2.5)	3.0 (0)
DASS - depression	7.60 (7.30)	4.5 (3.5)	1.0 (1.4)	9.4 (4.5)	2.7 (3.8)	3.5 (4.0)	8.50 (5.80)	3.4 (3.4)	2.7 (3.4)
DASS - anxiety	4.00 (2.45)	4.5 (3.5)	3.0 (2.8)	4.6 (2.5)	1.3 (1.2)	2.8 (4.2)	4.30 (2.36)	2.6 (2.6)	2.8 (3.5)
DASS - stress	7.80 (6.30)	3.5 (4.9)	1.0 (1.4)	11.0 (5.0)	3.3 (3.1)	4.0 (3.6)	9.40 (5.62)	3.4 (3.3)	3.0 (3.2)

Results – ATOP, DASS

	Varenicline Baseline N=5	Naltrexone Baseline N=5	Varenicline Follow Up 2 N=4	Naltrexone Follow Up 2 N=2
ATOP Psych mean (SD)	4.8 (1.9)	5.2 (1.6)	8.0 (1.6)	6.5 (2.1)
ATOP Physical mean (SD)	6.2 (1.9)	4.6 (2.7)	6.8 (3.0)	7.5 (0.7)
ATOP QoL mean (SD)	4.6 (1.7)	5.2 (2.6)	8.0 (1.8)	7.0 (1.4)
DASS - depression mean (SD)	9.4 (4.5)	7.6 (7.3)	3.5 (4.0)	1.0 (1.4)
DASS - anxiety mean (SD)	4.6 (2.5)	4.0 (2.4)	2.8 (4.2)	3.0 (2.8)
DASS - stress mean (SD)	11.0 (5.0)	7.8 (6.3)	4.0 (3.6)	1.0 (1.4)