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Psychiatry and Addictions Case Conference

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TREATING CO-OCCURRING DEPRESSION AND ALCOHOL USE DISORDER

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SPEAKER DISCLOSURES

- ✓ Any conflicts of interest?

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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OBJECTIVES

1. Review the epidemiology and relevant history of Major Depressive Disorder (MDD) and Alcohol Use Disorder (AUD)
2. Understand current clinical considerations and treatment models for Co-occurring MDD & AUD (MDD:AUD)
3. Review Assessment and treatment of Co-occurring MDD & AUD

EPIDEMIOLOGY & HISTORY – KEY STATISTICS

MDD

- NESARC-III (n=36,309) Cross-sectional Study 4/2012 – 6/2013
 - Highest in young white females with household incomes <\$20k
 - 80% more likely to have AUD (aOR 1.8, 95% CI, 1.63-2.01)
 - ~70% are treated during their lifetime

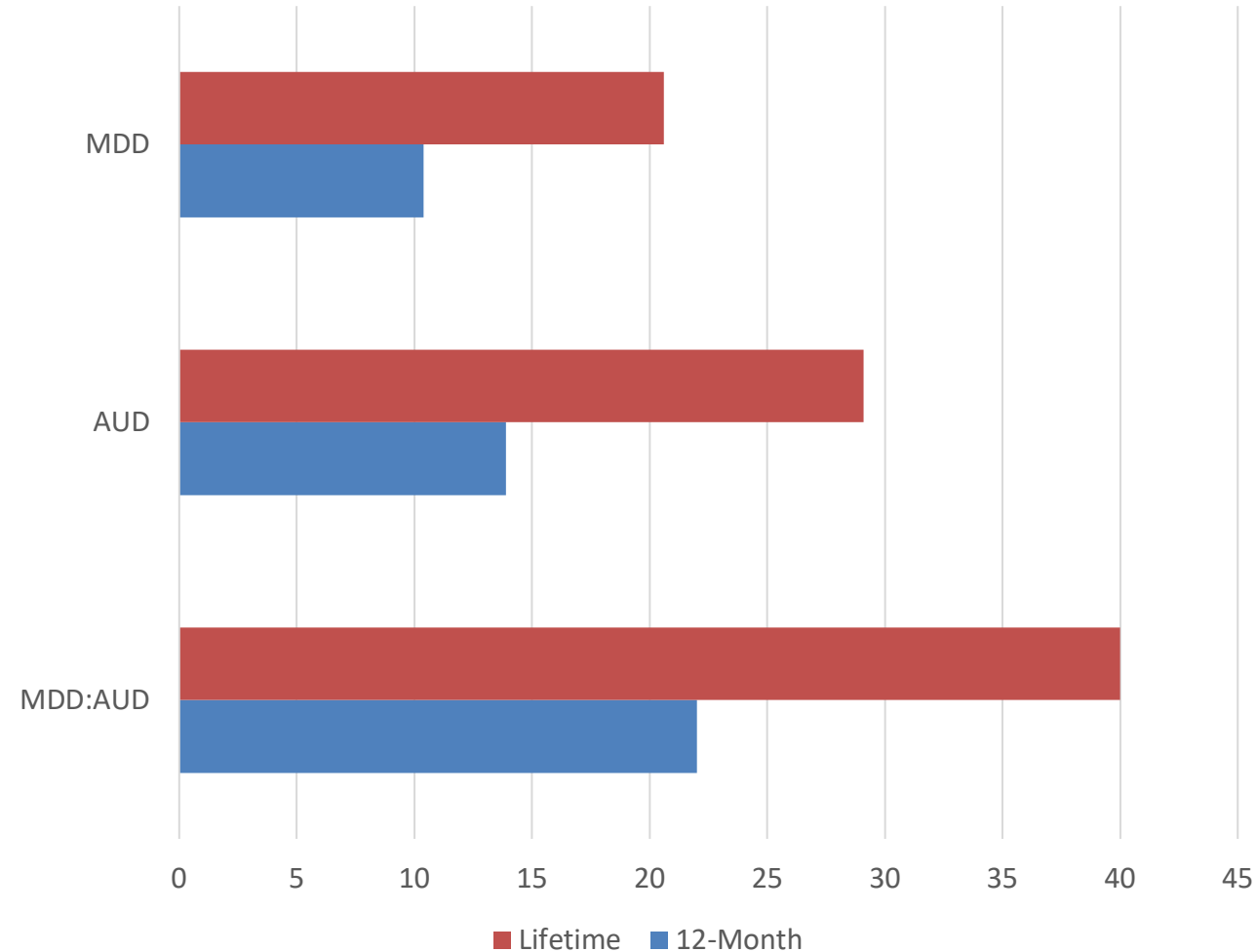
AUD

- NESARC-III (n=36,309) Cross-sectional Study 4/2012 – 6/2013
 - 12-month AUD = Men 2-3x > Women

MDD:AUD

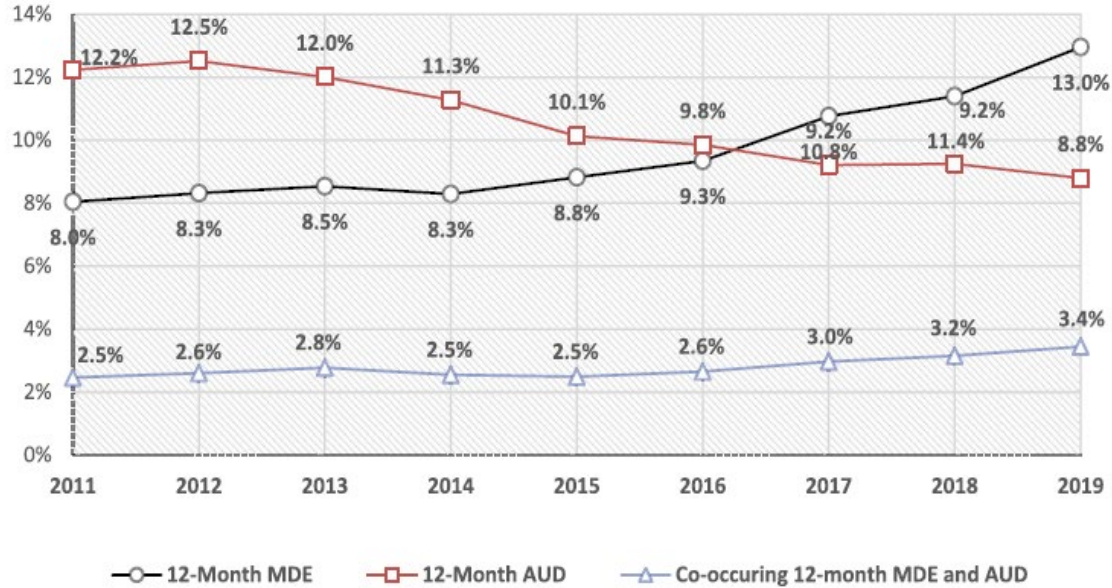
- MH:SUD is 7-35% in general population
- Highest rates among active duty/reserve military
 - MDD 4-23% vs 6-10% in GP
 - “Alcohol problem” 12-21% vs 4.7% in GP
 - Binge drinking 34%
 - Heavy drinking in last 30 days 9.8%
- Alcohol problem = M > F 3:1
- Heavy alcohol use = White > Black 2:1

Prevalence Rates (%)



TREATMENT TRENDS

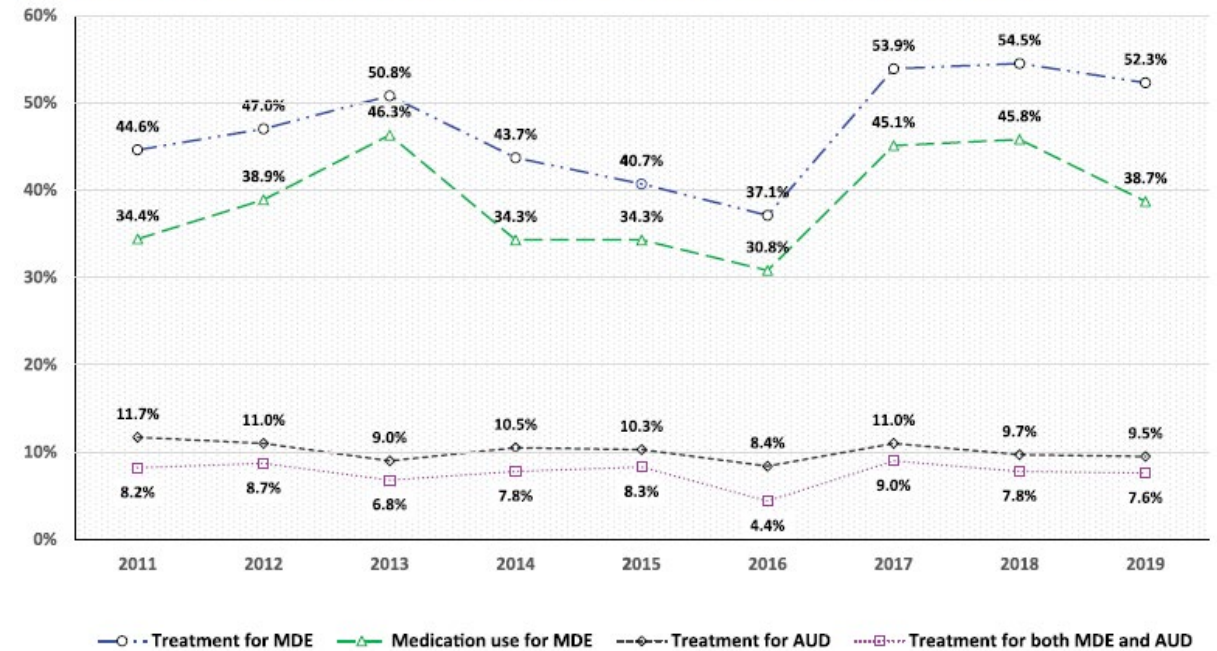
Trends in the 12-Month Prevalence of MDE, AUD, and Co-Occurring MDE and AUD Among Young Adults in the NSDUH, 2011–2019



2011 – 2019 Prevalence Trends in Young Adults

- Steady increase in 12-mo MDE, 8% to 13%
- Decrease in AUD, 12.2% to 8.8%
- Relatively stable COD, 2.5% to 3.4%

Trends in Treatment Use Among Young Adults With Co-Occurring 12-Month MDE and AUD



2011 – 2019 Treatment Trends in Young Adults with MDD:AUD

- MDE Treatment in MDD:AUD significantly increased, 44.6% to 52.3%
- Receiving medications for MDE in MDD:AUD significantly increased, 34.4% to 38.7%
- AUD Treatment in MDD:AUD remained stable, 9.5% to 11.7%
- MDD:AUD Treatment remained stable at <9%

TREATMENT DISPARITIES

- Race

- White > Latinx, Black, Asian/NHPIs
 - MDE, AUD, and MDD:AUD – $p < 0.001$
 - Latinx -- AOR 0.59/0.82/0.68
 - Black -- AOR 0.53/0.65/0.47
 - Asian/NHPIs -- AOR 0.59/0.54/0.53

- Age & Sex

- 18-21yo > 22-25yo
 - MDE 86% – AOR 1.86, $p < 0.001$
- F > M
 - MDE 86% – AOR 1.86, $p < 0.001$
 - MDD:AUD 28% – AOR 1.28, $p < 0.001$
- M > F
 - AUD 39% – AOR 1.39, $p < 0.001$

- Income

- MDE, MDD:AUD = <\$20,000 household income
- Household incomes <\$20k used more treatment for AUD and MDD:AUD than \$20k-\$50k and +\$75k

- Insurance

- Uninsured
 - AUD 11% more prevalent – AOR 1.11, $p < 0.001$
- Insured
 - 39% more treatment for MDE, but not AUD or MDD:AUD – AOR 1.39, $p < 0.05$

- Severity

- Severe impairment from MDD
 - Increased odds of receiving treatment for MDE, AUD, and MDD:AUD – AOR 2.51/2.07/2.49, $p < 0.001$

TREATMENT DISPARITIES & SOLUTIONS

- Barriers to treating MDD:AUD in young adults (18-22yo)
 - Unready to quit
 - Unaffordable
 - Treatment stigma
 - Uninformed about treatment locations
 - Poor fit with peer group
- Needed Treatments
 - Young adults
 - **Improved identification**
 - SBIRT in primary care and schools
 - School Health and Alcohol Harm Reduction Project (SHAHRP) > DARE
 - Alcohol Skills Training Program (ASTP)
 - Brief Alcohol Screening and Intervention for College Students (BASICS)
 - **Approachable treatment**
 - Harm reduction
 - Treatment programs that allow for developmentally normal behaviors
 - Peer recovery programs



AGENDA – UNDERSTANDING MDD:AUD

1. Review the epidemiology and relevant history of Major Depressive Disorder (MDD) and Alcohol Use Disorder (AUD)
- 2. Understand current clinical considerations and treatment models for Co-occurring MDD & AUD (MDD:AUD)**
 - Alcohol's relationship to depression
 - Cognitive impairment
 - Treatment models
 - Treatment outcomes
3. Review Assessment and treatment of Co-occurring MDD & AUD

UNDERSTANDING MDD:AUD – RELATIONSHIP

- **Depressive symptoms in childhood**
 - Decreased age of first drink
 - 2x odds of DSM-IV alcohol dependence in young adulthood
 - More likely to have MDD:AUD if having MDE, SI, and behavioral problems <13yo
- **AUD in young adults**
 - 3-4x suicide attempt risk
 - 50% more likely to have mood disorder
 - AUD responsible for 10% of disease burden related to COD
 - Higher prevalence of mood, anxiety, substance, and thought disorders
- **Similar age of onset, but AUD tends to present earlier than MDD**
 - 2x risk of developing second disorder (MDD \leftrightarrow AUD)
- **“Chick or the Egg?”**
 - Longstanding debate
 - Self medicating hypothesis
 - MDD \rightarrow Biopsychosocial consequences \rightarrow AUD
 - Gene-environment hypothesis
 - AUD \rightarrow Biopsychosocial consequences \rightarrow MDD
 - Male Monozygotic Twin studies
 - N=1874, Twins with lifetime MDD had 2.8x odds of AUD
 - N=3372, First twin with MDD associated with risk of second twin having MDD and MDD:AUD, but not AUD alone
 - Genome Wide Studies
 - SEMA3A gene variant associated with MDD:AUD in African Americans



UNDERSTANDING MDD:AUD – COGNITIVE IMPAIRMENT

- Cognitive impairment well known in MDD and AUD
- Impairments in executive functioning
 - Working memory
 - Attention
- Unclear if MDD:AUD cognitive impairment is unique
 - Attentional bias to alcohol related words
 - Impulsive correlates with severity of depression
 - Worse visual memory tasks
 - More subtle deficits in executive functioning compared to AUD
 - Other studies have found no difference when compared to AUD



UNDERSTANDING MDD:AUD – COGNITIVE IMPAIRMENT

- Study by Flores-Medina 2022
 - N=48
 - MDD:AUD = 17
 - MDD = 14
 - AUD = 17
 - Control = 17
 - Demographics
 - 20-55yo, depressed patients tended to be younger
 - Junior HS/HS educated
 - Neuropsychological & electrophysiological evaluations at baseline, then q14 days over 8 weeks
- HAMD, MADRS, BDI, ADS, OCDS given to appropriate patients
- Results:
 - MDD:AUD
 - Similar depression scores to MDD
 - Similar severity of alcohol dependence to AUD
 - Worst performance in most memory test, processing speeds, attention, and executive functioning
 - Fluoxetine 40mg treatment
 - MDD:AUD and MDD significant improvement on different memory tests
 - MDD:AUD improved in executive functioning in learning and cognitive flexibility

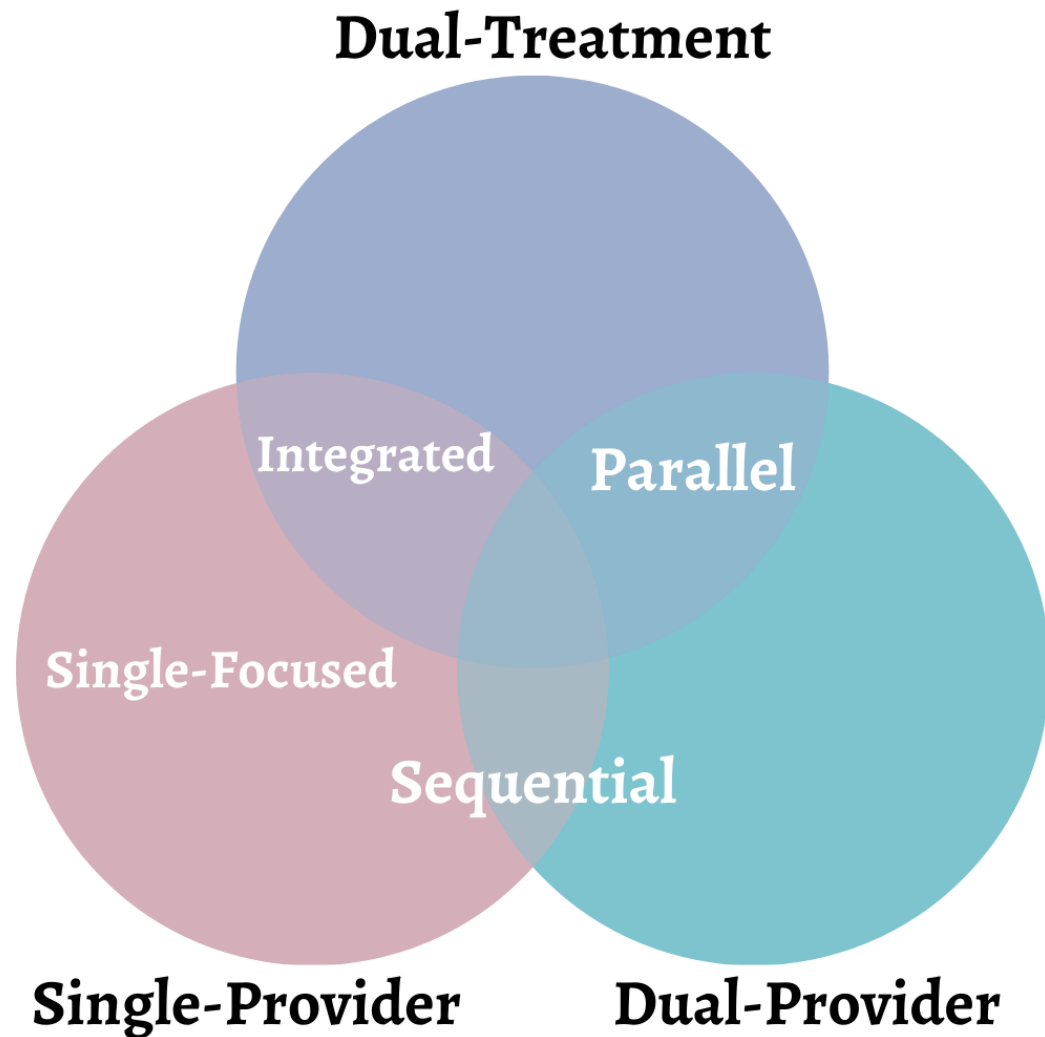
UNDERSTANDING MDD:AUD – TREATMENT MODELS

Single-Focused Treatment

- Treated primarily for either MDD or AUD
- Single provider

Sequential Treatment

- Treated primarily for one condition at a time
 - AUD --> MDD
- Single vs Double Providers



Parallel Treatment

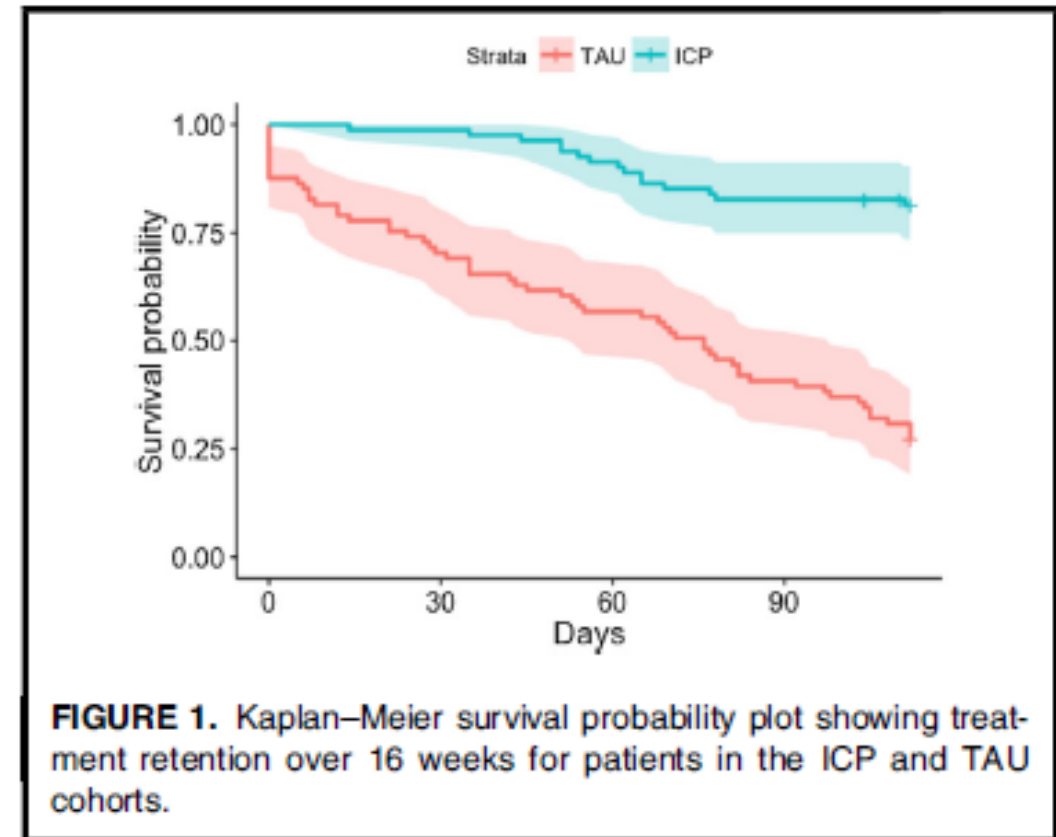
- Simultaneous treatment of MDD:AUD
- Double providers

Integrated Treatment

- Simultaneous treatment of MDD:AUD
- Single provider

UNDERSTANDING MDD:AUD – TREATMENT MODELS

- Non-randomized retrospective cohort study
 - Centre for Addiction and Mental Health (Toronto, CAN)
 - Developed Integrated Care Pathway (ICP) specifically for MDD:AUD
 - N = 81
 - Meds for MDD:AUD
 - Psychotherapy
 - 16 weeks
 - Compared to Treatment As Usual (TAU)
 - N = 81
 - Medications for either MDD, AUD, or MDD:AUD
 - Same providers and settings as before creation of ICP MDD:AUD
 - Results
 - ICP had significantly lower dropout rates at 16 weeks (18.5% vs 69.1%)
 - Both (ICP > TAU) significantly reduced heavy drinking days & standard drinks/week
 - ICP had significantly lower depressive symptoms
 - Effect Size Comparisons
 - (ICP vs TAU)
 - » Drinks/drinking day = 0.5
 - » Drinks/week = 0.4
 - » Drinking days/week = 0.3
 - » Heavy drinking days/week = 0.3
 - ICP compared to baseline symptoms
 - » Drinking patterns 0.9 – 1.1
 - » Depression (BDI & QIDS) ranged 0.8 – 0.9



UNDERSTANDING MDD:AUD – TREATMENT MODELS

- New Zealand systematic review, 2018
 - Examined effectiveness of therapy treatments specifically for MDD:AUD
 - Single-focused vs Parallel vs Integrated Models
 - 7 studies, none used sequential model
 - 3 Parallel, 4 Integrated, both compared to Single-Focused
 - None compared Parallel to Integrated head-to-head
 - Results:
 - Parallel:
 - Had overall greater number of significant outcomes (7/14) at follow up periods, but low to moderate quality studies
 - Concerns about non-randomization, concealment of allocation, protection against contamination
 - Integrated:
 - Worse outcomes (2/16) but had more “Reasonable” quality

Table 3. Number of follow-up time points with a significant intervention effect over the total number of follow-up time points for each study for both depression and alcohol outcome measures.

Study	Follow-ups with significant depression outcomes measures	Follow-ups with significant alcohol outcomes measures
Parallel versus single treatment (usual care)		
Brown (1997)	4/7 1/1 (on 2/3 outcomes)	3/7 2/2 (on 3/4 outcomes)
Brown et al. (2010)	1/4 (on 1/2 outcomes)	0/4
Watkins (2011)	2/2 (on 1/1 outcome)	1/1 (on 1/1 outcome)
Integrated versus usual care		
Morley (2016)	1/2 0/1	1/2 1/1 (on 3/6 outcomes)
Oslin (2003)	1/1 (on 2/3 outcomes)	0/1
Integrated versus single treatment (intervention)		
Baker (2010, 2014) ^a	0/6 0/5	0/6 0/5
Geisner (2015)	0/1	0/1

^aStudy demonstrated significant findings at 18-week follow-up. The table reflects findings at 36-month study outcomes.

UNDERSTANDING MDD:AUD – TREATMENT OUTCOMES

- COD have worse treatment outcomes, physical health, QOL, and increased risk of mortality
- MDD:AUD have shorter times to first drink and relapse (Greenfield et al.)
 - Cohort of AUD and MDD:AUD, hospitalized for AUD, followed 1yr
 - MDD:AUD had first drink 38 days vs 125 days for AUD
 - MDD:AUD had full relapse 41 days vs 150 days for AUD
 - If discharged without antidepressant, then all depressed patients relapsed in first 100 days
 - 20% discharged with SSRI abstinent at 1yr
 - No statistical difference in time to first drink between MDD vs Alcohol induced depression

AGENDA - ASSESSMENT & TREATMENT

1. Review the epidemiology and relevant history of Major Depressive Disorder (MDD) and Alcohol Use Disorder (AUD)
2. Understand current clinical considerations and treatment models for Co-occurring MDD & AUD (MDD:AUD)

3. Review Assessment and treatment of Co-occurring MDD & AUD

- How to assess for COD MDD:AUD
- Pharmacologic Treatment Options
- Psychotherapeutic Treatment Options

PATIENT ASSESSMENT

- Evaluation

- FHX, SUD history, comorbid medical illnesses, past medication trials and adherence history, suicidality, organization and cognition, chronic pain, multiple relationship issues, frequent job changes, legal difficulties
- PHQ9 for depression, AUDIT-C for at-risk use, DSM-5 for AUD
- Ask which problem they feel came first, depression or alcohol?

- Considerations

- Labs to follow alcohol use
 - Urinary Ethylglucuronide (UEtG) = Recent use
 - Phosphatidyl Ethanol = Moderate to heavy use
 - Carbohydrate Deficient Transferrin (%CDT) = Heavy, harmful use
- More likely to attempt suicide if MDD:AUD

TREATMENT - ANTIDEPRESSANTS

Antidepressants

- Antidepressants effectively mitigate quantity of alcohol use but sustained abstinence or remission are relatively low
- SSRI more effective than placebo in reducing depression sxms in COD, but more research is needed to compare effectiveness of active treatments
- Review of 33 studies of antidepressants in those with MDD:AUD showed low quality evidence with mixed results warranting further research

- New Zealand Meta Analysis (1980 – 2014)
 - MDD:AUD, MDD, and SIMD estimating changes in depression during treatment and antidepressant effectiveness
 - 22 studies met inclusion, then 11/22 were included with intention to treat samples
 - All studies reported large improvement in depressive symptoms (effect size 0.25), mostly in first 3-6 weeks
 - MDD:AUD had limited evidence for depression outcomes (effect size 0.08)

TREATMENT - ANTIDEPRESSANTS

- Promising combinations with positive outcomes for safely reducing both depression and alcohol symptoms in MDD:AUD
 - **Sertraline + NTX** (Pettinati et al)
 - Significantly higher abstinence (53.7%) compared to others (21.3%, 27.5%)
 - Significantly longer delay to heavy drinking relapse (98 days)
 - Non-significant depression scores, but favorable trend
 - **Escitalopram + Acamprosate** (Witte et al)
 - 50% MDD response
 - 42% MDD remission
 - Placebo had 36% for both (non-significant)
 - Significant reduction in #Drinks/week
 - No significant associations between changes in depression and alcohol use
 - **Citalopram + NTX** (Adamson et al)
 - Significant decreases in mood & drinking outcomes in both groups
 - ~70% vs ~60% Days Abstinent = Effect size 1.29
 - MADRS Depression = Effect size 2.30
 - However, not significantly different suggesting citalopram is not a useful adjunct
 - Well tolerated, well adhered
 - No difference in outcomes if MDD or SIMD
 - More %Days Abstinent if female taking NTX + Citalopram

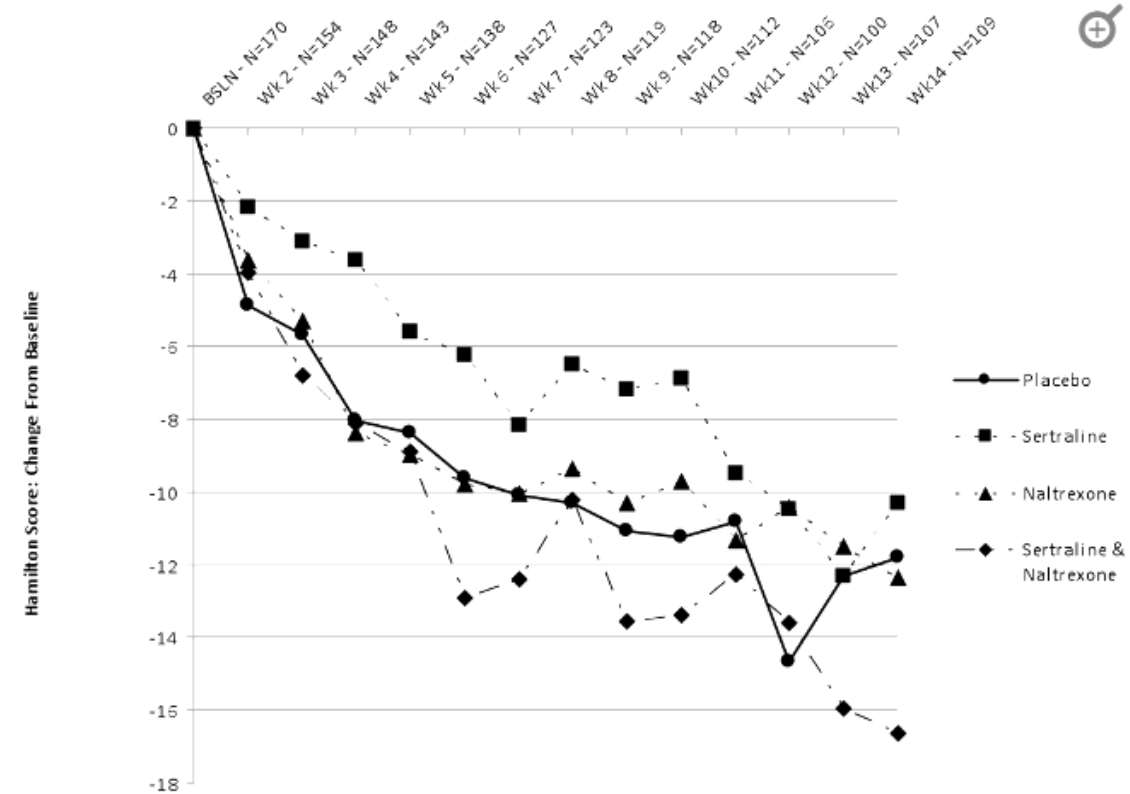


Figure 3

Change in scores on the Hamilton Rating Scale of Depression across treatment weeks for four medication conditions tested for treating co-occurring depression and alcohol dependence

TREATMENT - ANTIDEPRESSANTS

- Cochrane study (Agabio et al. 2018) of 33 studies (N=2242)
 - Antidepressants compared to...
 - Placebo = 22 studies
 - Psychotherapy = 2 studies
 - Other medications = 4 studies
 - Other antidepressants = 5 studies
 - Mean duration 9.9 weeks (3-26 weeks)
 - USA (18), Europe (12), Turkey (2), Australia (1)
 - 68% male, mean age 42yo
 - Settings
 - Outpatient = 18 studies
 - Inpatient = 9 studies
 - Both = 6 studies

- Antidepressants studied
 - **Sertraline** was most common
 - Others included:
 - Amitriptyline
 - Citalopram
 - Desipramine
 - Doxepin
 - Escitalopram
 - Fluoxetine
 - Fluvoxamine
 - Imipramine
 - Mianserin
 - Mirtazepine
 - Nefazodone
 - Paroxetine
 - Tianeptine
 - Venlafaxine
 - Viloxazine
- Outcomes had high degree of heterogeneity
- Conclusions
 - Low quality evidence for use of antidepressants in MDD:AUD
 - Moderate quality evidence for number of participants achieving abstinence from alcohol (but not duration) and reduced drinks per drinking day
 - Antidepressants had positive effect on some important MDD:AUD outcomes, but not others. Many of these positive effects disappeared after removing studies with high risk for bias
 - Overall, low risk of using antidepressants, especially SSRIs

TREATMENT – THERAPY MODALITIES

- **Motivational Interviewing (MI)**
 - Way of interacting with patient to evoke their own reasons to change behaviors
 - Studied in both mood and SUD, more recent literature supporting use in COD
 - MDD:AUD = Reduces #hospitalizations, decreases usage, and improves engagement with outpatient treatment
- **Cognitive Behavioral Therapy (CBT)**
 - Explores and reframes dysfunctional thoughts, beliefs, and assumptions
 - Improves %Days abstinent, decreases #drinks/day, improves depression symptoms
 - Digital options, lower barrier
- **Relapse Prevention Therapy (RPT)**
 - Builds insight into relapse patterns and strategies to avoid it
 - Explores and takes inventory of high-risk triggers, then uses CBT-based approaches to avoid triggers
 - Limited data for MDD:AUD, but robust for AUD
- **Contingency Management (CM)**
 - Operant conditioning, provides rewards for not using
 - Requires lab testing to confirm abstinence (Urinary Ethylglucuronide)
 - Limited data specifically for MDD:AUD, but overall positive effects for SUD
- **12 Step Models (AA/NA etc) & 12 Step Facilitation**
 - 12 Step programs have positive data for AUD
 - Some supporting data for a heterogeneous COD group, higher rates of abstinence
 - 12 Step Facilitation is a professionally led treatment by clinicians that encourage engagement with 12 step programs
- **Data suggests combining medications and therapy provides the best outcomes**
 - No clear treatment algorithm

SUMMARY KEYPOINTS

- MDD:AUD is prevalent and leads to worse outcomes. Prevalence has remained relatively steady
- While depression tends to affect more white young females from households <\$20,000 and alcohol use disorders occur more in men, active duty/reservist military patients carry the heaviest burden of co-occurring MDD:AUD
- We need further research to determine the best treatment model for MDD:AUD, but integrated model seems to be preferred if clinical infrastructure can support
- Sertraline + NTX may be the best combination currently. Escitalopram + Acamprosate is a reasonable alternative
- MI and CBT are best placed to address both conditions, but several other therapy modalities can also help

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THANK YOU!

