Treatment of Comorbid Alcohol Use Disorders and Depression
Depression often comorbid with alcohol dependence

1.6x higher rate of alcohol dependence in depressed subjects

Depressed subjects with alcohol dependence have complicated course of depression

Subjects with concurrent disorders seek treatment more
Alcohol dependence prolongs the course of depression
Persistence of depression during abstinence is a risk for relapse to heavy drinking
Very mixed findings on whether antidepressants are effective in improving depression in those with concurrent alcohol use disorder

- <12 well-controlled antidepressant trials with depressed alcohol-dependent patients
  - Pettinati reviewed 8 RCT’s of pharmacotherapy for depression with comorbid EtOH dependence → 6 showed antidepressants superior to placebo in depression but only 3 showed antidepressants superior to placebo in reducing EtOH use
  - Antidepressants have not been proven effective for reducing EtOH and drug use in those without concurrent depression
PICO Question

- **P** - Subjects with depression and alcohol use disorder
- **I** - Treated with antidepressant
- **C** - Compared to those subjects treated with placebo
- **O** - Report improved depression and decreased EtOH consumption
PUBMED Search:

- Depression AND
- Alcohol use disorder AND
- Comorbid AND
- Antidepressant
  - = 90 total (30 reviews)

- RCT
  - = 7 total
Analyzed whether antidepressants in conjunction with a medication used that directly affects drinking may be necessary for successful treatment.

Compared mood and drinking outcomes of Sertraline and Naltrexone combination vs placebo for both mood and EtOH consumption.

Prediction that those on Naltrexone and Sertraline would achieve complete abstinence, delay relapse to heavy drinking and show reduced depressive symptoms.
Open-Label study of 14 depressed alcohol dependent patients given Naltrexone (50mg) with SSRI → decreased drinking and mood improvement

Placebo-controlled study did not find an advantage in adding Naltrexone to decrease drinking in 74 Sertraline-treated depressed, EtOH dependent adults
Exclusion Criteria:

- Other substance use dependence
- Bipolar, Schizoaffective or psychotic disorders
- Already on antidepressant
- Needed more psych meds than an antidepressant
- Pregnant/breastfeeding

Inclusion Criteria:

- 12 or more drinks per week
- Drank on 40% of the 90 days before study
- 3 days of abstinence before study
- HAM-D of 10 or higher
- MDD and EtOH dependence via SCID-P
Weekly CBT

Week 1: Naltrexone 50 mg Qday; gradually titrated up to 100 mg Qday after 4 days

Week 2: Sertraline 50 mg Qday; gradually titrated up by 50 mg Q3 days until reached 200 mg Qday

Week 13: Naltrexone decreased to 50 mg Qday

Week 14: Sertraline decreased to 100 mg Qday

Chose higher doses than FDA-recommended given results from COMBINE study
Study Measures

- Breathalyzer tests at each visit
- Weekly HAM-D
- Weekly Alcohol Timeline Followback method (memorable life events and calendar for up to 90 days)
Study Outcomes

- **Drinking Outcomes**
  - Total abstinence during 14 week trial (all days)
  - Time to relapse until heavy drinking day (average # days before heavy drinking day)

- **Depression Outcomes**
  - No depression during last 3 weeks of study (HAM-D < 9)
  - HAM-D scores in last week
<table>
<thead>
<tr>
<th>Variable</th>
<th>Sertraline Plus Naltrexone (N=42)</th>
<th>Naltrexone (N=49)</th>
<th>Sertraline (N=40)</th>
<th>Placebo (N=39)</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td>Age (years)</td>
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<tr>
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<td>15.4</td>
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<tr>
<td>Hamilton Depression Rating Scale score (past 30 days)</td>
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<td>N</td>
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<td>33</td>
<td>67.3</td>
</tr>
<tr>
<td>%</td>
<td>57.1</td>
<td>33</td>
<td>67.3</td>
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<td>18.4</td>
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<td>Married</td>
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<td>33.3</td>
<td>17</td>
<td>34.7</td>
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<tr>
<td>Cigarette smoking (&gt;5 cigarettes per day)</td>
<td>33</td>
<td>78.6</td>
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<td>Socioeconomic status (middle to upper)</td>
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<td>59.5</td>
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<td>67.3</td>
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<tr>
<td>Family history of alcohol abuse</td>
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<td>64.3</td>
<td>38</td>
<td>77.6</td>
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<tr>
<td>Family history of alcohol and/or drug abuse</td>
<td>19</td>
<td>45.2</td>
<td>29</td>
<td>59.2</td>
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<tr>
<td>Family history of depression</td>
<td>23.6</td>
<td>71.0</td>
<td>22.9</td>
<td>77.3</td>
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<tr>
<td>Mean days of drinking (past 30 days)</td>
<td>25.0</td>
<td>63.0</td>
<td>24.4</td>
<td>72.5</td>
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Treatment Attendance & Medication Adherence

- 60% of CBT sessions
- 3.5 support group meetings attended
- Average Naltrexone dose 91 mg Qday
- Average Sertraline dose 170 mg Qday
- Total adherence was 87%
- Total treatment course was 80%
- 26% adverse outcomes ➔ most for inpatient detox
  - Rate of adverse events significantly lower with combination group (12%) vs other groups (26-37%)
Results

- Ave age = 44
- Most Men (62%) and Caucasian (65%)
- Ave yrs of EtOH use = 21
- Ave # of prior tx = 2
- Mean HAM-D at initiation = 23.1
Depression Outcomes

- No depression during last 3 weeks
- No statistical significance

- Mean end-of- tx HAM-D
- No statistical significance (6.9 vs 9.9 of others)
- However, those in combo group were less depressed
No advantage in tx with Sertraline alone; rather, there was a slower rate for mood improvement than compared to other groups

Little advantage in prescribing antidepressants alone for depressed pts with EtOH dependence
Drinking Outcome Results

- **Total Abstinence**
  - 54% of combined group abstinent (vs 23.8% of 3 other groups combined)

- **Time to Relapse to Heavy Drinking**
  - Longer time to relapse in combination group (64 days vs 42.2 days)
Patients with co-occurring major depression and alcohol dependence might be optimally treated with therapies that address each condition.

More depressed- EtOH dependence pts tx’d with combination achieved complete abstinence and significantly delayed relapse to heavy drinking.

Less adverse events in combination group.

Patients with both disorders benefit from tx with both for EtOH disorders.
Limitations & Strengths

**Limitations**
- All received CBT
- Setting was outpatient substance dependence facility
- Short-term measurements only
- Subjects had less of a problem with depression than with EtOH?
- Not generalizable to other SSRIs or EtOH meds

**Strengths**
- Large sample size
- One of the first trials of this type
Examine difference in outcome with Celexa between MDD + SUD vs MDD - SUD

MDD often presents with concurrent substance use disorders (SUD) thought to impair antidepressant response

Often delay antidepressant tx until demonstrate sustained sobriety

STAR*D: 2876 adults with MDD tx’d with Celexa (divided into +/- SUD)

- SUD (30%) compared to no SUD (70%)
- SUD group had reduced rates of remission + increased times to reach remission
- SUD group had greater psychiatric adverse events and hospitalization rates
Methods

- STAR*D (www.clinicaltrails.gov #NCT00021528)
- RCT to define effectiveness of Celexa in nonpsychotic MDD who had had unsatisfactory outcome on past antidepressant
- SUD split into 3 groups → 18% had EtOH use disorder (29% with some type of SUD)
Outcome Measures

- SUD determined by PDSQ (psychiatric diagnostic screening questionnaire--self-report 126 item scale for past 6 months→ those who endorsed sx only)
- Time to remission based on QIDS-C (quick inventory of depressive symptomatology) and on HRSD (Hamilton rating scale)
## Results - Demographics

<table>
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<tr>
<th>Demographic</th>
<th>Substance use disorder</th>
<th>( \rho )</th>
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<tr>
<td></td>
<td>Absent ( N = 2006 ) (70.8%)</td>
<td>Present ( N = 829 ) (29.2%)</td>
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<tr>
<td></td>
<td>( % )</td>
<td>( % )</td>
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<tr>
<td>Setting – primary care</td>
<td>38.9</td>
<td>35.5</td>
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<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>77.6</td>
<td>73.8</td>
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<tr>
<td>African-American</td>
<td>16.7</td>
<td>19.0</td>
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<tr>
<td>Others</td>
<td>6.3</td>
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<td>Ethnicity – Hispanic</td>
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<td>11.4</td>
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<td>Sex – female</td>
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<td>51.6</td>
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<td>Marital status</td>
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<td>Never married</td>
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<td>Married</td>
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<td>Widowed</td>
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<td>Employment status</td>
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<td>Unemployed</td>
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<td>Public insurance</td>
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<tr>
<td>No insurance</td>
<td>31.7</td>
<td>41.8</td>
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</table>
Note- only look at +/- SUD

+SUD: male, single, unemployed, no insurance, younger, less income, less education
Results - Remission & Response Rates

- SUD subgroups showed difference in time to remission
  - +SUD: 22.5% remission (OR of 42% less likely to remit) on QIDS
  - -SUD: 33.4% remission on QIDS
  - +SUD: 20% remission on HRSD
  - -SUD: 28% remission on HRSD

Remission and response status by substance use.

<table>
<thead>
<tr>
<th>Substance use</th>
<th>QIDS-SR16 remission</th>
<th>p-value</th>
<th>QIDS-SR16 response</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>OR (95% CI)</td>
<td></td>
<td>%</td>
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<tr>
<td>None (N=2006)</td>
<td>33.4</td>
<td>0.0201</td>
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<td>47.2</td>
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<tr>
<td>Alcohol only (N=536)</td>
<td>35.5</td>
<td>1.16 (0.99 - 1.34)</td>
<td></td>
<td>47.2</td>
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<tr>
<td>Drug only (N=155)</td>
<td>28.4</td>
<td>0.79 (0.55 - 1.13)</td>
<td></td>
<td>45.8</td>
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<tr>
<td>Both (N=138)</td>
<td>22.5</td>
<td>0.58 (0.38 - 0.87)</td>
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<td>43.5</td>
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<tr>
<td>Total (N=2835)</td>
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Outcome

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<tr>
<th>Exit QIDS-SR16</th>
<th>Mean (SD)</th>
<th>Alcohol (N=536) Mean (SD)</th>
<th>Drug (N=155) Mean (SD)</th>
<th>Both (N=138) Mean (SD)</th>
<th>Total (N=2835) Mean (SD)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>9.1 (5.8)</td>
<td>8.8 (5.8)</td>
<td>10.5 (6.7)</td>
<td>10.1 (5.6)</td>
<td>9.1 (5.9)</td>
<td>0.0025</td>
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<tr>
<td>Change in QIDS-SR16</td>
<td>-7.1 (5.9)</td>
<td>-7.1 (5.8)</td>
<td>-6.5 (6.5)</td>
<td>-7 (5.2)</td>
<td>-7.1 (5.9)</td>
<td>0.7282</td>
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<tr>
<td>QIDS-SR16 change (%)</td>
<td>-43.1 (35.1)</td>
<td>-44.3 (34.4)</td>
<td>-37.9 (38.4)</td>
<td>-39.1 (34.8)</td>
<td>-42.9 (35.2)</td>
<td>0.4261</td>
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</table>
Both groups had an average of 42% reduction in self-report depression symptoms.

Both groups had an average of 27% remission on clinician-rated scale (47% response on self-report and 33% remission on self-report).
Discussion

- 1/3 of subjects in STAR*D at level 1 endorsed concurrent SUD sx (19% EtOH, 6% drug, 5% both)
- Modest improvement in depression with Celexa (47% response, 33% remission)
- Antidepressants may be equally beneficial in depressed pts with or without SUD; many MDD +SUD groups have baseline indicators of more severe depression, chance of response is generally equal to those without SUD
However, the rate of remission is what varies between groups:

- There are differences in rates of and times to remission
  - MDD only: 33.4% remission rate
  - MDD + EtOH: 35.5% rate
  - MDD + drugs: 22.5% rate

Antidepressants may be equally beneficial in depressed pts with or without SUD

While MDD+SUD may have more severe depression, chance of response is generally equal to those -SUD
Limitations & Strengths

**Limitations**
- Open-label
- Short-term (12 wks)
- PDSQ to identify SUD (FP 34%)
- Did depression tx affect SUD?
- What type of SUD?
- No period of abstinence before study

**Strengths**
- Large sample
- Primary and psychiatric care settings
- Broad inclusion
- No advertisements
Double-blind placebo-controlled trial of fluoxetine in adolescents with comorbid major depression and an alcohol use disorder
Addictive Behaviors 2009; 34:905-909

- Compare 12 wk efficacy of SSRI + CBT/MET vs placebo +CBT/MET
- STAR*D found that MDD and concurrent SUD group had earlier age of onset of MDD
- Adolescent onset depression associated with higher level of comorbid SUD than adult-onset
- Most EtOH use disorders begin in adolescence
- Prevalence of EtOH dependence peaks between 18-20 yo
- First double-blind placebo-controlled study of Fluoxetine in adolescents with comorbid MDD and EtOH use disorder
- Many RCTs demonstrated efficacy of Fluoxetine in adolescent MDD without SUD
- Lack of studies with adolescents and comorbid MDD and EtoH use disorder → reluctant to treat with antidepressant
Methods

- Recruitment via WPIC treatment program or media advertisements
- **Inclusion criteria:** 15-20yo, EtOH abuse or dependence at baseline AND MDD at baseline, >10 drinks per month prior to baseline, HAM-D >15 at baseline
- **Exclusion criteria:** bipolar, schizoaffective, schizophrenia, cardiac/thyroid/neurological/renal/hepatic disease, tx with antidepressants in month prior to study, SUD other than nicotine and cannabis, hx IVDA, pregnancy
Treatment

- All subjects given placebo or 10mg Fluoxetine, increased to 20mg daily after 2 weeks
- EtOH use and sx severity ratings Qweek x 4 weeks then biweekly thereafter
- $20 per assessment
- CBT for MDD and EtOH use disorder
- MET for EtOH use disorder
  - Total of 9 therapy interventions (none on week 5,7,11)
Study Measures

- Brethlyzer tests at each visit
- Timeline Follow-back Method for EtOH measurements (#drinks per day, #drinking days, #heavy drinking days)
- Self-report depressive sx with BDI
  - Remission of depression: BDI<8
- Observer rated depressive sx with HAM-D-27
Results

- 118 initially enrolled → 50 met inclusion criteria & 50 included in outcome analysis
- No discontinuations due to SE/ no SI
- 3 drop-outs from placebo group (each after 6 weeks) due to urging from study team due to persistent severe depressive sx
  - These 3 immediately treated with open-label Fluoxetine and all 3 showed decreased depressive and EtOH use sx
- No major differences between tx groups (Fluoxetine group slightly less depressed at baseline)
  - 22 men, 28 women
  - 86% Caucasian, 1% African-American
<table>
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<tr>
<th></th>
<th>Placebo (n = 26)</th>
<th>Fluoxetine (n = 24)</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Sex (% female)</td>
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<td>50.0%</td>
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<tr>
<td>Ethnic (% white)</td>
<td>88.5%</td>
<td>83.3%</td>
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<tr>
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<td>HAM-D 27</td>
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<tr>
<td>Current major depression symptom count (DSM)</td>
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<tr>
<td>Drinks per day</td>
<td>3.06</td>
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<tr>
<td>Drinks per occasion</td>
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<tr>
<td>Days of alcohol use per week</td>
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<tr>
<td>Heavy drinking days per week</td>
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<td>Current major depression symptom count</td>
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<tr>
<td>Drinks per day</td>
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<td>Drinks per occasion</td>
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<tr>
<td>Days of alcohol use per week</td>
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<tr>
<td>Heavy drinking days per week</td>
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<td>1.21</td>
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Results

- **Depressive sx:** BDI and HAM-D-27 decreased for both placebo and Fluoxetine groups at significant levels.

- **EtOH use:** decreased for both groups & # heavy drinking days significantly associated with improvement on BDI at weeks 6 & 12.
Discussion

- Fluoxetine did not demonstrate efficacy for treating either depressive sx or EtOH-related sx
- In both tx groups, significant within-group improvement noted for both depressive sx and level of drinking
- Link between depressive sx and level of EtOH consumption in comorbid adolescents
- Psychological intervention should be considered first-line for this population
- Offer pharmacotherapy for those that don’t respond to psychological interventions alone
Limitations & Strengths

LIMITATIONS
- Limited medication efficacy/dose
- Small study size
- Non-representative sample
- CBT/MET unlikely in clinical practice
- Placebo effect in adolescents

STRENGTHS
- First double-blind placebo-controlled study of this type