The use of CBT to prevent transition to psychosis in patients at ultra-high risk

a Journal Club presentation brought to you by Lisa Valentine
Recent interest in early detection and intervention in prodromal states of psychosis

Yung et al (1996) defines operational criteria to identify four subgroups at ultra-high risk (dubbed ARMS)

- Using these criteria, 40% of their high-risk sample developed psychosis over the following 9 months
- But other studies estimate conversion rates much lower

Interventions studied to date include:
- Risperidone + CBT
- Olanzapine
- Eicosapentoic acid
- CBT alone (this is the one this presentation is about)
So, you’re probably wondering…

- Why it would be swell if CBT worked:
  - Antipsychotics have side effects, especially troubling given false positives
  - Stigma of taking psychiatric medications
  - Possible effects of antipsychotics on developing brains of adolescents
  - Might also target depression and anxiety

- And why it might actually work:
  - Allows for normalization of the interpretations that patients make
  - Help patients to generate and evaluate alternative explanations
  - Decatastrophizes their fears of impending madness
  - Helps patients test out appraisals using behavioral experiments.
Without further ado…

In patients meeting criteria for at-risk mental state according to the PACE criteria, does cognitive behavioral therapy as compared to treatment as usual* decrease the risk of transition to psychosis?

*No such thing
Dear Patients meeting PACE Criteria,

We don’t care if CBT works for you.

Love,

The United States of America
Hypotheses

- Cognitive therapy will significantly reduce the transition rate in comparison with treatment as usual.

- Cognitive therapy will:
  - significantly reduce the proportion of patients who need to be prescribed antipsychotic medication,
  - reduce the likelihood of meeting criteria for a DSM-IV diagnosis of a psychotic disorder, and
  - reduce the severity of the presenting subclinical symptoms.
Study Design: The Patients

- Recruited from primary care teams, student counseling services, accident and emergency departments, specialist services (e.g. community drug and alcohol teams, child and adolescent psychiatry and adult psychiatry services) and voluntary sector agencies (e.g. care-giver organizations)

- Inclusion criteria (based on the PACE Criteria for ARMS)
  - AS: attenuated psychotic symptoms (using PANSS)
  - BLIPS: brief limited intermittent psychotic symptoms (using PANSS)
  - First degree relative with psychotic disorder + deterioration in functioning (using GAF or GHQ)
  - Schizotypal personality disorder (using SCID) + deterioration in functioning

- Exclusionary criteria:
  - Outside the range of age 16-36 (maximum risk period)
  - Current or past use of an antipsychotic medication
Outcome Measures

- Transition to psychosis as defined by:
  - Meeting PACE Criteria based on PANSS ($\geq 4$ on hallucinations, $\geq 4$ on delusions, $\geq 5$ on conceptual disorganization), symptoms at least several times/week, duration of $>1$ week OR
  - Prescription of an antipsychotic medication from an independent practitioner
  - Probably DSM-IV diagnosis from a consultant psychiatrists masked to treatment status, rated using vignettes that were prepared from case notes and assessment records by the assessors.
Study Design: Methods

- EDIE trial (Early Detection and Intervention Evaluation)
  - Single blind (rater)
  - Randomized: stratified by gender and genetic risk
  - Controlled

- Two groups
  - Both received case management services
  - Control group received monitoring, i.e. initial assessment + one year of monthly assessment with PANSS

- Intervention group received
  - A maximum of 26 sessions of CT over 6 months
  - Approach depended upon the problem list agreed upon by patient and therapist
    - If psychotic symptom, then focused on culturally unacceptable interpretations that people with psychosis make for events, in addition to their responses to such events and their beliefs about themselves, other people, and control strategies.
    - If not, then other appropriate model was employed
    - A general model of emotional dysfunction was also used (helpful for patients with multiple presenting problems)
48 met AS criteria  
6 met BLIPS criteria  
4 had family hx + functional decline
Statistically speaking…

- Intention to treat analysis (except for 2)
- Missing data were recorded as such, except for transition to psychosis
- Transition to psychosis was estimated to be NONE if no data
- Logistic regression analysis used to compare transition between two groups, while controlling for potential confounders (age, gender, family history, initial PANSS positive scores)
- Number needed to treat also reported
- ANOVA used to examine effects of cognitive therapy on positive psychotic phenomena
- Multiple regression analysis performed on 12-month GHQ and GAF scores
The Results!

- For transition as defined by PANSS, main effect of CT was significant (OR= 0.4, 95% CI 0.01-0.71, P=0.028)
  
  i.e. there’s a 96% reduction in the odds of making a transition in the CBT group compared to monitoring alone, after adjustment for age, gender, family history, and baseline PANSS score.

  - NNT to prevent PANSS-defined transition = 6

- For transition as defined by prescription of an antipsychotic, main effect of CT also significant (OR= 0.6, 95% CI 0.01-0.57, P=0.014)

  - NNT to prevent antipsychotic-defined transition = 5

- For transition as defined by DSM-IV criteria, main effect of CT also significant (OR= 0.04, 95% CI 0.01-0.57, P=0.019)

  - NNT to prevent DSM-IV criteria-defined transition = 5

Table 2  Outcome measures

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>PANSS transition</th>
<th>Antipsychotic medication</th>
<th>DSM–IV psychosis diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Monitoring</td>
<td>5 (22)</td>
<td>7 (30)</td>
<td>6 (26)</td>
</tr>
</tbody>
</table>
There are even more results!

- Significant effect of group on mean PANSS positive scores, with CT resulting in significantly fewer positive symptoms over time than monitoring.

- No significant effect of group on 12 month GAF and GHQ scores (authors note, however, that many GAF and GHQ scores were missing.)
The authors conclude…

A six month package of CT is effective in reducing transition to psychosis over a 12 month period in a high-risk, help-seeking population. The high rate of consent to randomization (95%) as well as low withdrawal rate (14%) implies that the population deems this an acceptable intervention.
Assets and Liabilities

- **Study Strengths**
  - Wide variety of referral sources
  - Using validated criteria to select study subjects
  - Narrow exclusionary criteria
  - Randomized
  - Controlled
  - Single blinded (er, kind of…)
  - Results likely are robust given that CBT found to be significant on all outcome measures

- **Study Limitations**
  - Small sample size
  - Uneven group sizes after randomization
  - Need to exclude 2 participants due to later finding out they met exclusionary criteria
  - Lots lost to follow up
  - Missing data sets
  - Does not distinguish CBT from nonspecific therapeutic effects
  - The Er, Kind of…
Two further scales were included in assessment
- Metacognitions Questionnaire
- Sociotropy-Autonomy Scale

These were included in order to test explanatory hypotheses about the action of CT.

In addition to monthly assessments for the first 12 months, participants were monitored at every 6 months with PANSS for the next 2 years.

They tried everything to reach people.

In the end, only 27 patients were successfully followed up (47%)
- 49% of CT group vs. 43% of monitoring group (not significant)

Where data were unavailable, PANSS-defined transition was assumed to have not occurred; all one-year data were carried forward (so this assumed that all those who didn’t follow up who had not made transition at 1 year also had not made transition by 3 years).
Drum roll please…

- Logistic regression analysis were conducted with the 3 year follow-up data as dependent variable (gender, family hx, age, and baseline PANSS positive subscales were used as predictor variables).

- Using PANSS-defined transition as dependent variable, the main effect of CT was not significant.
  - But, when baseline PANSS positive subscale scores, metacognitive beliefs about uncontrollability, and sociotropy entered as predictor variables, the main effect of CT was significant (OR = 0.03; 95% CI 0.01-0.64, P =0.026).
  - These latter 2 variables were thought to be significant because they would indicate psychological vulnerabilities that would be amenable to treatment.

- Using prescription of antipsychotic medication as the dependent variable, the main effect of CT was significant (Or= 0.13, 95% CI 0.02-0.76, P= 0.024).

- Using DSM-IV diagnosis as dependent variable, the main effect of CT was not significant.
Authors suggest that medication prescription may be most reliable indicator of transition because of arbitrary PANSS cut-offs and both PANSS- and DSM-IV-defined transition are self-reported, whereas medication prescription was corroborated by medical records.

BUT: prescription of antipsychotic is getting increasingly nonspecific.

Would have been helpful to know more about medication dose/duration/polypharmacy.

Same weaknesses as original study.
Questions?
Hypotheses

- Patients receiving CBT will have a lower conversion rate to psychosis
- Patients receiving CBT will
  - have a greater reduction in symptoms with regard to prodromal symptoms, depression, and anxiety, and
  - have greater reduction in indicators of poor functioning
Study Design: The Patients

- Recruited from family physicians, student counselors, and community mental health teams and practitioners. This included advertisements on radio, public transit, and local newspapers.

- Inclusion Criteria
  - Met Criteria of Prodromal States (COPS) using the Structured Interview for Prodromal Symptoms (SIPS)

- Exclusionary Criteria
  - Met criteria for any current or lifetime axis I psychotic disorder
  - Prior history of treatment with an antipsychotic
Outcome Measures

- Primary outcome of transition to psychosis was determined by the Presence of Psychotic Symptoms (POPS).
- At 6, 12, and 18 months, participants also completed the Calgary Depression Scale (CDSS), Social Anxiety Scale (SAS), Social Interaction Anxiety Scales (SIAS), and Social Functioning Scale (SFS).
- Where possible, both the therapist and client versions of the Working Alliance Inventory-Short Form (WAI-SF) were used twice during the study, once in the early portion (sessions 3-5) and once in the later portion (sessions 10-20).
Study Design: Methods

- Randomized (groups stratified by sex and severity of prodromal sx)
- Single-blinded (raters)
- Six month treatment phase and 12 month follow-up phase
- Two groups, both treated by master’s level clinicians
  - Control group received up to 20 sessions of supportive therapy over a 6-month period
    - Finding out how the week had been, deal with crises and give advice to help with any immediate problems.
    - No CBT techniques. Rather, focused on listening, reflecting and empathizing, and demonstrating uncritical acceptance and genuineness.
    - Psychoeducational information about psychosis and managing stress offered.
  - Intervention group received up to 20 sessions of CBT over a 6 month period. CBT format was based upon the EDIE trial.
    - Treatment fidelity was monitored.
- Comprehensive assessments conducted at baseline, 6, 12, and 18 mos.
• 41% with MDD
• 43% with anxiety disorder
• 10% with alcohol abuse
• 19% with cannabis abuse
## Table 1
Baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CBT (N = 27)</th>
<th>ST(N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>20.8 (4.51)</td>
<td>21.1 (3.74)</td>
</tr>
<tr>
<td>Years of education SD</td>
<td>12.7 (3.46)</td>
<td>12.9 (2.41)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (35.3)</td>
<td>18 (35.3)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (17.7)</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Currently working, n (%)</td>
<td>13 (25.5)</td>
<td>11 (21.6)</td>
</tr>
<tr>
<td>Racial background, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (25.5)</td>
<td>16 (31.4)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (3.9)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (13.8)</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (9.8)</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>Marital status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single, never married</td>
<td>24 (47.1)</td>
<td>23 (45.1)</td>
</tr>
<tr>
<td>Cohabiting with a significant other</td>
<td>3 (5.9)</td>
<td>1 (2.0)</td>
</tr>
</tbody>
</table>
*Current student, n (%)          | 22 (43.1)    | 13 (25.5)  |
| Comorbid diagnosis              |              |            |
| Mood disorder, n (%)            | 13 (25.5)    | 13 (25.5)  |
| Anxiety disorder, n (%)         | 9 (17.7)     | 9 (17.7)   |
| Alcohol abuse, n (%)            | 2 (3.9)      | 3 (5.9)    |
| Cannabis abuse, n (%)           | 5 (9.8)      | 5 (9.8)    |

*p < 0.05.
You can leave your stats on...

- They expected a conversion rate of 40% in the control group with a 50% reduction for the active treatment group.
- Sample size estimates for two-tailed tests with a significance level of 0.05 and a power of 80% were 83 per group, based on the need to detect the difference expected above.
- Kaplan-Meier plots with log-rank test employed to compare the difference the rate of conversion.
- Mixed effects models for longitudinal data were used to compare the mean difference in positive and negative symptoms on the SOPS, depression, anxiety, and social functioning over the 6, 12, and 18 month follow-up period in order to accommodate missing data and account for intra-participant correlation over time.
The Results Are In!

- There were 3 conversions to psychosis in the ST group as compared to zero in the CBT group
  - Based on Kaplan Meier survival estimates, there was a higher likelihood of conversion to psychosis for the ST group (log rank test p=.059), but with small sample size and zero events, that ain’t saying much.
- There was a rapid decline in SOPS positive symptoms for both groups, which was statistically significant (but without significant difference in change rate between the two groups)
  - There was a significant time effect within CBT group with most improvement occurring the first three months.
- No significant differences in negative symptoms or social functioning
- No significant differences in CDSS except for ST group between baseline and 6 months
- No significant differences between groups on SIAS, though it improved in both over time (not to the level of significance)
- Significant time effect for the ST group between baseline and 18 months on the SAS
Average number of sessions was 12, but 31% received less than 7.

Most of CBT ended up focusing on assessment and engagement and less was spent on core CBT strategies such as alternative solutions and explanations, and metacognitions.

Per the WAIS-SF, the average score indicated a positive relationship between therapists and clients.
Discussion

- The authors ponder:
  - Maybe both treatments are equally effective (CBT is no better)
    - But patients didn’t really get enough CBT
    - The therapists “were not doctoral level CBT specialists” (wicked burn)
    - Perhaps the patients had different needs
  - Maybe neither treatment is effective
    - This is pretty tough to determine when there’s no “treatment as usual”
    - People may have gotten better with tincture of time
  - The study is underpowered
  - The conversion rate was way lower than anticipated
The Good and the Bad

○ **Strengths**
  - Randomized
  - Control group to weed out nonspecific effects of therapy
  - Single-blinded
  - Tested for treatment fidelity
  - Narrow exclusionary criteria
  - Multiple sources of referral
  - More evenness between numbers in groups

○ **Limitations**
  - Underpowered
  - Possibly not enough treatment given to elicit change from CBT
  - Lack of treater expertise?
  - High drop-out rate
Questions?
Study Design: Aim and Patients

- To assess the feasibility and efficacy of cognitive therapy to reduce psychopathology in people at ultra-high risk (UHR) for psychosis in Korea

- Recruited from a research clinic of the Green Program for Recognition and Prevention of Early Psychosis project

- Inclusion criteria: BIPS, APSS, or GRDS as assessed by the Structured Interview for Prodromal Symptoms.

- Exclusionary criteria: None reported

BIPS: brief intermittent psychotic; APSS: attenuated positive symptoms state; GRDS: genetic risk and deterioration state
Study Design: Methods

- Psychopathology measured by PANSS, BDI and SIPS
- Participants received 10 weekly sessions of cognitive therapy based on a highly-structured therapy manual, targeting prodromal symptoms of psychosis, based on Morrison’s work.
  - Normalizing the catastrophic interpretations of impending illness
  - Reducing distress and fear
  - Targeting the socio-cognitive biases of externalizing attribution style and jumping-to-conclusion bias, helping participants to generate and evaluate alternative explanations and test out appraisal biases using behavioral experiments
  - Keeping patients connected with external reality
  - Highlighting importance of belief about self/self-esteem and metacognitive belief
- Therapists trained via seminars and received supervision, but no formal measure of treatment fidelity was employed.
A paired t-test employed to compare pre- and post-scores on outcome measures.

Within-group effect sizes were calculated using the mean difference divided by the pooled standard deviation (in accordance with similar previous studies).
The Numbers

- Total subjects: 22
- Female subjects: 11
- Mean age: 19.4 years
- Mean education: 12.7 years
- Mean IQ: 12.9
- Number of subjects low-dose atypical antipsychotic*: 8 (44.4%)
- Subjects completing 10 sessions: 18
- Dropouts lost to follow-up: 4 (18.2%)

* Less than 200mg/day of chlorpromazine equivalent dose
The Results!

- Significant reductions in PANSS, SIPS subscores and BDI scores
- 55% of UHR subjects who completed the therapy showed a clinically significant (30%) reduction in PANSS positive symptoms score
- In antipsychotic naïve patients, there were significant reductions in measures of psychopathology except for the BDI, SIPS disorganized and SIPS general symptoms
- Two subjects progressed to psychosis after 10-12 months follow up of the 10 sessions.

**TABLE 2.** Means (standard deviations) and effect sizes for outcome variables before and after treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-CT†</th>
<th>Post-CT†</th>
<th>t</th>
<th>P-value</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>25.78 (8.27)</td>
<td>13.78 (8.11)</td>
<td>3.618</td>
<td>0.007</td>
<td>1.47</td>
</tr>
<tr>
<td>SIPS-positive</td>
<td>11.44 (2.97)</td>
<td>6.75 (3.43)</td>
<td>5.438</td>
<td>&lt;0.0001</td>
<td>1.46</td>
</tr>
<tr>
<td>SIPS-negative</td>
<td>11.28 (5.42)</td>
<td>6.81 (4.96)</td>
<td>4.814</td>
<td>&lt;0.0001</td>
<td>0.86</td>
</tr>
<tr>
<td>SIPS-disorganized</td>
<td>3.56 (2.28)</td>
<td>2.50 (2.28)</td>
<td>2.471</td>
<td>0.026</td>
<td>0.46</td>
</tr>
<tr>
<td>SIPS-general</td>
<td>8.06 (5.19)</td>
<td>4.69 (3.98)</td>
<td>3.036</td>
<td>0.008</td>
<td>0.73</td>
</tr>
<tr>
<td>PANSS-positive</td>
<td>16.11 (3.71)</td>
<td>11.24 (3.56)</td>
<td>4.874</td>
<td>&lt;0.0001</td>
<td>1.34</td>
</tr>
<tr>
<td>PANSS-negative</td>
<td>16.94 (4.82)</td>
<td>11.59 (4.47)</td>
<td>5.653</td>
<td>&lt;0.0001</td>
<td>1.15</td>
</tr>
<tr>
<td>PANSS-general</td>
<td>35.44 (8.37)</td>
<td>21.53 (8.77)</td>
<td>6.213</td>
<td>&lt;0.0001</td>
<td>1.62</td>
</tr>
</tbody>
</table>

†Data are presented as mean ± standard deviation (SD). Cohen's d = mean (pre) – mean (post)/SD (pooled).
BDI, Beck Depression Inventory; CT, cognitive therapy; PANSS, Positive and Negative Syndrome Scale; SIPS, Structured Interview for Prodromal Syndromes.
The authors conclude that 10 sessions of CT for individuals meeting criteria for UHR for psychosis can significantly reduce psychopathology, including positive, negative and depressive symptoms, and the within-group effect sizes indicated large treatment benefits.

Comprehensive cognitive therapy for UHR subjects may be feasible to apply in non-Western cultures.
Every Rose Has Its Thorn

- **Strengths**
  - Narrow exclusionary criteria
  - Even gender ratio
  - Highly structured CBT
  - Majority of subjects completed all ten sessions

- **Limitations**
  - Maybe too narrow (inclusion of subjects on antipsychotics)
  - Very small
  - No control group
  - No measure of therapy fidelity
  - Some results are based off of an even smaller sub-sample
  - Little discussion of conversion rate
In conclusion...

- Cognitive therapy seems to be a promising intervention for patients at ultra-high risk for psychosis both for the reduction of prodromal symptoms as well as to reduce the risk of conversion to psychosis.

- However, current available studies are fraught with high drop-out rates, design flaws, and difficulty with blinding.

- Further studies are needed to gauge the long-term effectiveness of cognitive therapy for this population.

- Further direct comparisons of CT to psychotropic management of the ultra-high risk state would also be useful, not only with respect to conversion, but also with respect to patients’ view of their treatment.
Questions?