Combining Psychotherapy and Medication in Psychiatric Disorders: Evidence for a Strategic Approach

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Grand Rounds, April 3rd, 2013
Objectives

- Review the evidence for the short and long-term efficacy of combining pharmacotherapy and psychotherapy for psychiatric disorders.

- Review the logic of current approaches to combination treatments.

- Present arguments for alternatives to current strategies that are designed to optimize cost/benefit risk/benefit ratios.
Bergin and Garfield's Handbook of Psychotherapy and Behavior Change

- The “Bible of Psychotherapy”
- Comprehensive summaries of the literature
- Review the evidence for the efficacy of combining psychotherapy and medications
- What are the best strategies for implementing combination treatments?
Why Combine?

- Medication and empirically supported psychotherapies are efficacious monotherapies

- Significant residual symptoms remain after treatment
  - (Kocsis et al., 2000; Judd et al., 2003; Yonkers, Bruce, Dyck & Keller, 2003)

- Relapse and recurrence are common
  - (Beshai, Dobson, Bockting & Quigley, 2011; Gitlin et al., 2001; Post et al., 2003; Yonkers, Bruce, Dyck & Keller, 2003)

- Combos might improve shorter and longer-term outcomes
In most cases, combination treatments result in significant, incremental benefits in acute response.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Treatments</th>
<th>Effect Size</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depression</td>
<td>Med + Psychtx &gt; Med</td>
<td>$d = 0.31$</td>
<td>Cuijpers et al. (2009)</td>
</tr>
<tr>
<td>Anxiety Disorders</td>
<td>Med + CBT &gt; Placebo + CBT</td>
<td>$g = 0.59$</td>
<td>Hofman et al. (2009)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Med + CBT &gt; Med</td>
<td>$d = 0.40$</td>
<td>Wykes et al. (2008)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Med + Psychtx &gt; Med</td>
<td>Relapse 40% reduced</td>
<td>Scott et al. (2007)</td>
</tr>
</tbody>
</table>
Combined Treatment

- Combined treatment is recommended by major clinical guidelines (NICE, APA), particularly for severe, chronic or treatment resistant cases.
Clear benefits?

- Logic: two treatments are better than one

- Combo Tx increases costs and risk
  - Pharmacotherapy:
    - Side effects
    - Toxicities
    - Cost of maintenance
  - Psychotherapy:
    - Increased acute cost
    - Possible negative effects
    - Opportunity costs

- Optimize cost/benefit and risk/benefit ratios
Hidden Cost of Combination Treatment

- Information costs

- 2 hypotheses of combo treatment benefit
The “Magnitude” Hypothesis of Combination Treatment Efficacy

![Bar graph showing percent improvement in Psychotherapy and Psychotherapy + Medications for two patients.](image-url)
The “Matching” Hypothesis of Combination Treatment Efficacy

![Bar Graph]

- **Patient 1** (matched to psychotherapy)
- **Patient 2** (matched to medications)
Combo Efficacy Derived from “Matching”?

- Type unknown prior to treatment
- Match responders are given both treatments but respond because they receive the “correct” treatment
- Additional treatment without additional benefit
- Information costs:
  - Missed opportunity to learn about monotherapy response
  - Useful information for long-term management:
    - Illness characteristics
    - Maintenance
    - Recurrence
- “De-personalized” medicine
Longer-term Outcomes

- Many combo studies are short-term acute trials
- Durability of acute advantage is in question
  - Anxiety disorders
- Limited data on maintenance strategies
Evidence for Combination Treatment

- Examples from major disorders
  - Schizophrenia
  - Anxiety disorders
  - Major depression
Schizophrenia

- Antipsychotics are the mainstay therapy
- Effective for reducing positive symptoms
- Outcomes poor overall
  - 30% poor initial response (Lehman et al., 2004)
  - Poor medication adherence (Lieberman et al., 2005)
  - Relapse is common
- Heterogeneous disorder that is not well suited to a “one size fits all” approach (McGorry et al., 2010)
Psychotherapy for Schizophrenia

- Used as adjunctive treatment to antipsychotics

- CBT for psychosis
  - Re-appraise the power and source of hallucinations (e.g., internal vs. external)
  - Evaluate the veracity of delusions
  - Address motivational and other deficits (Guadiano, 2006; Tarrier, 2010)

- Family psychoeducation
  - Improve coping & reduce stress
  - Reduce conflict and expressed emotion
Pharmacotherapy + CBTp

- Persistent, medication resistant positive symptoms (Sensky et al., 2000)
A Randomized Controlled Trial of Cognitive-Behavioral Therapy for Persistent Symptoms in Schizophrenia Resistant to Medication

Tom Sensky, PhD, FRCPsych; Douglas Turkington, FRCPsych; David Kingdom, MD, MRCPsych; Janine L. Scott, MD, FRCPsych; Jonathan Scott, MRCPsych; Ronald Siddle, BSc, RMN, RGN; Madeline O’Carroll, MSc, RMN; Thomas R. E. Barnes, MD, FRCPsych

**Background:** Research evidence supports the efficacy of cognitive-behavioral therapy in the treatment of drug-refractory positive symptoms of schizophrenia. Although the cumulative evidence is strong, early controlled trials showed methodological limitations.

**Methods:** A randomized controlled design was used to compare the efficacy of manualized cognitive-behavioral therapy developed particularly for schizophrenia with that of a nonspecific befriending control intervention. Both interventions were delivered by 2 experienced nurses who received regular supervision. Patients were assessed by blind raters at baseline, after treatment (lasting up to 9 months), and at a 9-month follow-up evaluation. Patients continued to receive routine care throughout the study. An assessor blind to the patients’ treatment groups rated the technical quality of audiotaped sessions chosen at random. Analysis was by intention to treat.

**Results:** Ninety patients received a mean of 19 individual treatment sessions over 9 months, with no significant between-group differences in treatment duration. Both interventions resulted in significant reductions in positive and negative symptoms and depression. At the 9-month follow-up evaluation, patients who had received cognitive therapy continued to improve, while those in the befriending group did not. These results were not attributable to changes in prescribed medication.

**Conclusion:** Cognitive-behavioral therapy is effective in treating negative as well as positive symptoms in schizophrenia resistant to standard antipsychotic drugs, with its efficacy sustained over 9 months of follow-up.

*Arch Gen Psychiatry. 2000;57:165-172*
Pharmacotherapy + CBTp

- Persistent, medication resistant positive symptoms (Sensky et al., 2000)
- Relapse prevention (Gumley et al., 2003)

**Fig. 3.** Kaplan-Meier plot of time to relapse for cognitive behaviour therapy (CBT) and treatment as usual (TAU).
Pharmacotherapy + CBTp

- Persistent, medication resistant positive symptoms (Sensky et al., 2000)
- Relapse prevention (Gumley et al., 2003)
- Negative symptoms (Grant et al., 2011)
Family Therapy

- Primary target is relapse prevention
- Family Therapy vs. control treatments (Pharoah, Mari, Rothbone & Wong, 2010)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Relative Risk of Relapse (Family Therapy vs. Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>0.55</td>
</tr>
<tr>
<td>18 months</td>
<td>0.64</td>
</tr>
<tr>
<td>24 months</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Combination Treatment in Schizophrenia

- Typically superior to standard care
- Recommended by major treatment guidelines (APA, NICE, PORT)
Combined Treatment for Schizophrenia

- Fairly circumscribed set of options:
- Heterogeneity of illness & treatment response
- Pharmacotherapy has drawbacks
- Is this sequence is appropriate for all groups?
Med-free Recovery from Psychosis

- Indications that a subgroup of individuals can recover without long-term maintenance

- Placebo response rates in antipsychotic trials > 25% (Kemp et al., 2010; Kinon, Potts, & Watson, 2011)

- A significant proportion (≈ 30%) of individuals with schizophrenia have long-term stable recoveries (Jobe & Harrow, 2005)

- Substantial portion of these recover without continued pharmacotherapy (Harrow & Jobe, 2007; Rappaport, 1978)

- Patients randomized to no-medication conditions have better long-term outcomes (Carpenter et al., 1977; Prien et al., 1968, 1971; Rappaport, 1978)
Managing Heterogeneity in Early Psychosis

- Medication delay + intensive psychosocial management
  - Agnews State Hospital Project (Rappaport et al., 1978)
  - Soteria project in San Francisco (Mosher & Menn, 1978)
  - Soteria-Berne project (Ciompi et al., 1992)
  - Acute Psychosis Integrated Treatment (API) in Finland (Lehtinen et al., 2000)
  - Parachute Project in Sweden (Cullberg et al., 2002)
Acute Psychosis Integrated Treatment (API)

- First 3 weeks of admission:
  - Antipsychotics not started whenever possible
  - Further delayed if positive response to psychtx
- Psychosocial treatment
  - Intensive family, individual and group therapy
  - Regular meetings and follow-up
  - Patient involved in all activities, including tx planning
  - Maintain a “psychotherapeutic attitude”
- Not a “no treatment” condition
API Trial

- 6-site non-randomized trial in Finland
  - 3 sites: API (n = 84)
  - 3 sites: standard care (n = 51)
- DSM-III-R, non-affective psychosis (first episode)
- Followed over 2 years

Results

<table>
<thead>
<tr>
<th></th>
<th>Experimental</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroleptic-free over 2 years</td>
<td>42.9%</td>
<td>5.9%</td>
</tr>
</tbody>
</table>
## API Results

### Table VIII. Two-year outcome by site; proportions by percentage.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Experiment</th>
<th>Control</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 2 weeks in hospital during 2 years</td>
<td>50.8</td>
<td>25.6</td>
<td>41.5</td>
<td>0.011</td>
</tr>
<tr>
<td>No psychotic symptoms during last year</td>
<td>58.2</td>
<td>41.0</td>
<td>51.9</td>
<td>0.088</td>
</tr>
<tr>
<td>Employed</td>
<td>32.8</td>
<td>30.8</td>
<td>32.1</td>
<td>0.826</td>
</tr>
<tr>
<td>GAS score 7 or more</td>
<td>49.2</td>
<td>25.0</td>
<td>40.2</td>
<td>0.019</td>
</tr>
<tr>
<td>Retained grip on life</td>
<td>65.7</td>
<td>55.3</td>
<td>61.9</td>
<td>0.291</td>
</tr>
</tbody>
</table>
Bola, Lehtinen, Cullberg and Ciompi (2009)

- Review of med delay studies
- Outcome at 2-3 years
  - Effect size: $r = 0.17$ (med delay > TAU)
- Subgroup of individuals can recover with limited (or no) pharmacotherapy
- Ascertain group membership through a stepped strategy
Review

Who needs antipsychotic medication in the earliest stages of psychosis? A reconsideration of benefits, risks, neurobiology and ethics in the era of early intervention

S.M. Francey b,d, B. Nelson a,b,d, A. Thompson a,b,d, A.G. Parker a, M. Kerr a,d, C. Macneil b,d, R. Fraser b,d, F. Hughes b,d, K. Crisp b,d, S. Harrigan a,d, S.J. Wood d,f, M. Berk a,b,c,d,e, P.D. McGorry a,b,d,*

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c Department of Psychiatry, University of Melbourne, Geelong, Australia
d Department of Clinical and Biomedical Sciences, Barwon Health, University of Melbourne, Geelong, Australia
e Mental Health Research Institute, Parkville, Victoria 3052, Australia
f Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne, Victoria 3052, Australia
Anxiety Disorders
Anxiety Disorders

- Efficacious monotherapies for acute treatment:
  - Medications
  - CBT

- Room for improvement:
  - Acute response rates ≈ 50%
  - Relapse rates 24% over 2 years
Combination Therapies in Anxiety

- Evidence for Acute Advantage for Combo Tx:
  - Panic disorder (Furukawa et al., 2006)
  - Social Anxiety (Blanco et al., 2010)
  - OCD (Hohagen et al., 1998)
  - PTSD (Schneier et al., 2011)

- Combo tx benefits:
  - Small (often not clinically significant)
  - Confined to subgroups (OCD)
Durability of Combo Therapies in Anxiety

- Medication might interfere with the enduring effect of CBT
- Evidence from 3 trials:
  - Marks et al. (1993) - panic
  - Barlow et al. (2000) - panic
  - Haug et al. (2003) - social anxiety
Marks et al. (1993)

- Panic disorder
- Four conditions:
  - Exposure + Alprazolam
  - Exposure + Placebo
  - Relaxation + Alprazolam
  - Relaxation + Placebo
- 8 weeks acute treatment
- 43 week medication-free follow-up
Sustained Response and Relapse in Marks et al. (1993)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Responded &amp; Relapsed</th>
<th>% Sustained Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP+ALP</td>
<td>35%</td>
<td>62%</td>
</tr>
<tr>
<td>EXP+PBO</td>
<td>9%</td>
<td>91%</td>
</tr>
<tr>
<td>RLX+ALP</td>
<td>22%</td>
<td>79%</td>
</tr>
<tr>
<td>RLX+PBO</td>
<td>6%</td>
<td>94%</td>
</tr>
</tbody>
</table>
Barlow et al. (2000)

- Panic disorder
- Four conditions:
  - CBT + Imipramine
  - CBT + Placebo
  - CBT
  - Imipramine
- 12 weeks acute treatment
- 2 year medication-free follow-up
Sustained Response and Relapse in Barlow et al. (2000)

<table>
<thead>
<tr>
<th>Group</th>
<th>% Responded &amp; Relapsed</th>
<th>% Sustained Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT+IMP</td>
<td>32%</td>
<td>25%</td>
</tr>
<tr>
<td>CBT+PBO</td>
<td>41%</td>
<td>8%</td>
</tr>
<tr>
<td>CBT</td>
<td>40%</td>
<td>8%</td>
</tr>
<tr>
<td>IMP</td>
<td>38%</td>
<td>18%</td>
</tr>
</tbody>
</table>

% responded & relapsed
% sustained response
Mechanism of Interference in Anxiety Tx

- **Suppression of fear-related cognitions** (Foa, Franklin, and Moser, 2002)
- **Learning does not generalize across medication discontinuation** (Otto et al., 2005)
- **Suppression of acute cortisol secretion** (Otto, McHugh, & Kantak, 2010)
Alternatives to Simultaneous Combination

- Monotherapy non-response?
- Sequenced approaches (augmentation)
  - Add-on psychotherapy
  - Add-on medications
Add-on Psychotherapy

- Simultaneous vs. Sequential
  - Simultaneous:
    - Foa et al. (2005)
    - OCD
    - Four conditions (N=122):
      - ERP + Clomipramine
      - ERP
      - Clomipramine
      - Placebo
    - 12 weeks acute treatment
Foa et al. (2005)

Add-on Psychotherapy

- Sequential:
  - Simpson et al. (2008)
  - OCD
  - Partial responders to SRI
    - 12 weeks, met adequate trial criteria
  - 2 conditions (N=111)
    - Exposure and Response Prevention
    - Stress Management Training
  - 8 weeks of treatment
Simpson et al. (2008)

FIGURE 2. Change in OCD Symptom Severity After Augmentation With CBT

Add-on Psychotherapy

- 17 positive studies (Rodrigues et al., 2011)
- Add-on CBT less susceptible to interference?
- Normalization of cortisol response (Otto, McHugh, & Kantak, 2010)
Add-on Medications

- Common clinical strategy
- Limited & equivocal evidence
  - 5 studies (3 positive, 2 negative)
Augmentation

- Little is known about long-term efficacy
- Comparisons between Augmentation and Simultaneous Combination
  - \( N = 0 \)
Anxiety Disorders

- Monotherapy is recommended
- Sequenced approach for non-response
  - Efficacy benefit?
  - Information benefit
Major Depression
Major Depression

- Efficacious monotherapies
  - Psychotherapy (CBT, IPT, BDT)
  - Antidepressant medications
  - Essentially equivalent
- Acute response rates ≈ 50%
- Relapse/recurrence: 40-85%
- CBT > Medications (dc’ed) in preventing relapse
Combo Treatment in Depression

- Combo > Medications alone ($d = 0.31$)
  - Cuijpers, Dekker, Hollon, & Andersson (2009)

- Combo > Psychotherapy alone ($d = 0.35$)
  - Cuijpers, van Straten, Warmerdam, & Andersson (2009)
Hollon et al. (2005) Review – Acute Response

Combination Treatment in Practice

Combination Treatment in Depression

- Efficacious in randomized trials
- Worth cost and risk?
- Advantages of non-simultaneous combos?
Sequencing Strategies

- Multiple combo augmentation strategies
  - Most find positive results
    - Acute response
    - Relapse prevention

- Most compare augmentation to TAU

- Frank et al. (2000)
  - 2 approaches to combining IPT and Meds
  - Successive cohort study
Frank et al. (2000)

- Condition 1: IPT + Imipramine (simultaneous)
  - Augmentation with perphenazine, lithium, or T₃
- Condition 2: IPT + SSRI augmentation
  - Multiple augmentation points

<table>
<thead>
<tr>
<th>IPT</th>
<th>Non-response</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>&lt; 33% HAMD reduction</td>
<td>2x/week IPT</td>
</tr>
<tr>
<td>Week 6</td>
<td>&lt; 25% HAMD reduction</td>
<td>Augment with SSRI</td>
</tr>
<tr>
<td>Week 8</td>
<td>&lt; 50% HAMD reduction after 2x/week IPT</td>
<td>Augment with SSRI</td>
</tr>
<tr>
<td>Week 12</td>
<td>&lt; 50% HAMD reduction</td>
<td>Augment with SSRI</td>
</tr>
<tr>
<td>Week 24</td>
<td>Absence of remission</td>
<td>Augment with SSRI</td>
</tr>
</tbody>
</table>
Frank et al. (2000) Results

- Sequential > Simultaneous (remission)

<table>
<thead>
<tr>
<th></th>
<th>Simultaneous</th>
<th>Sequential</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd Step Remission</td>
<td>66.1%</td>
<td>28.9%</td>
</tr>
<tr>
<td>1st Step Remission</td>
<td>66.1%</td>
<td>49.7%</td>
</tr>
</tbody>
</table>
Frank et al. (2000)

- Not randomized
- Different medications

What might be going on here?
  - Time
  - Timing – ready to benefit from meds?
  - Instillation of hope & confidence
    - Rule-based augmentation

A better way to think about combinations?
Fava and Ruini’s (2002) “Sequential Model”

- Theory-guided sequencing of treatment
- Treated to response with medications
- Meds tapered, pt. switched to well-being therapy (CBT; Fava, 1999)

“Sequential model” advantages:
- (a) alleviate residual symptoms
- (b) prevent relapse without maintenance medications
"Sequential Model" Results - Relapse

Fava et al., 1996, 1998a

Fava et al., 1998b, 2004

Sequential Model Results - Relapse

- Sequential
- TAU

Post 4 years 6 years

Post 2 years 6 years

*
Theory Guided Sequencing

- Advantages:
  - Specific guidance for how & when to deploy treatments
  - Maximize benefit of each treatment & minimize potential weaknesses

- Disadvantages:
  - Currently limited to medication first approach
  - Little guidance in case of first stage non-response
Sequential Combos in Practice

- CoBalT Study: Add-on CBT
  - Primary care patients in the UK (N = 469)
  - Minimum 6 weeks on an antidepressant
  - BDI-II ≥ 14
  - 12-18 sessions of CBT
  - Assessments at 6 & 12 months
CoBalT Study: Add-on CBT

Non-sequenced Combo Treatment in Practice

Advantages of Sequential Combos

- Limits over-treatment
  - Limits costs
  - Limits risks
- Possible efficacy benefits
- Provides information on effective treatment
- Intensive treatment held in reserve
- Rational method of handling heterogeneity
Disadvantages of Sequential Combos

- Evidence base
  - No comparisons with simultaneous combos
  - Appropriate pathways not established
    - Initial treatment
    - Timing of augmentation or switch
    - Maintenance strategies

- Institutional barriers
  - Availability of empirically supported psychtx
  - Pressure to provide maximum treatment
  - Patient preference
Recommendations for Research & Practice

- RCT of different combination pathways
Acute Phase

- CBT
  - Continue CBT
  - MED Augment
  - CBT Augment

- MED
  - Continue MED
  - CBT Augment

- CBT+MED
  - Continue CBT
  - MED Augment
  - CBT Augment

Continuation Phase

- d/c CBT
  - d/c CBT + cont MED
  - d/c CBT + PBO

- cont MED
  - PBO
  - d/c CBT + cont MED
  - d/c CBT + PBO

Follow-up

- Naturalistic Follow-up (No treatment)
Recommendations for Research & Practice

- Implement guidelines for combination treatment into practice
  - Continuous outcome monitoring
    - “measurement based practice” (Shelton & Trivedi, 2011)
  - Develop rules regarding treatment steps
- Outcomes vs. usual care
- Refine steps and rules of algorithm
- Work to overcome barriers
- Deploy our current treatments in a rational & strategic manner to improve outcomes
Questions?
Combination Treatment

- Combo = 2nd most common outpatient strategy
  - Medication alone: 57.4%
  - Psychotherapy alone: 10.5%
  - Combination treatment: 32.1%  (Olfson & Marcus, 2010)