Nonpharmacologic Interventions for Treatment-Resistant Depression

Public Meeting – December 9, 2011

New England CEPAC

- Goal: To improve the application of evidence to guide practice and policy in New England
- Method:
  - Core evidence: AHRQ review
  - ICER develops supplementary report with information on
    - New published literature
    - Policy landscape: coverage policies, clinical guidelines
    - Cost-effectiveness and budget impact

New England CEPAC

- CEPAC deliberation produces recommendations and votes on:
  - Comparative clinical effectiveness of alternative management options
  - Comparative value of these options
- CEPAC recommendations designed to support:
  - Patient/clinician education
  - Clinical guideline development
  - Medical policy (e.g., benefit design, coverage, payment)

Agenda

- Introductions (10-10:15)
- Evidence presentation (10:15-10:45)
- Q & A and CEPAC deliberation (10:45-12:00)
- Public Comment (12:00-12:30)
- Lunch (12:30-1:00)
- Votes and Recommendations (1:00-2:00)
- Roundtable on Implementation (2:00-3:20)
- Close (3:20-3:30)

EVIDENCE PRESENTATION

Outline

- Summary of AHRQ review
- New evidence following AHRQ review
- Clinical guidelines/coverage policies
- Comparative value analyses
  - Budgetary impact
  - Cost-effectiveness

SUMMARY OF AHRQ REVIEW

AHRQ Review*

- Evidence stratified into three "tiers":
  - Tier 1: Patients failing 2+ adequate trials of antidepressant drugs
  - Tier 2: Patients failing 1+ adequate trials of antidepressant drugs
  - Tier 3: Probable TRD, but number of prior treatment failures unspecified
- Results presented here include data from ALL tiers

*Gaynes BN et al. AHRQ Comparative Effectiveness Review #33.

TRD Management Options

- Electroconvulsive Therapy (ECT):
  - Available since 1930s, use in depression “grandfathered”; typically reserved for most severe cases given intensity of treatment, impact on cognition, and other side effects
- Repetitive Transcranial Magnetic Stimulation (rTMS):
  - FDA-approved in 2008 for use in TRD patients who have failed 1+ trials of antidepressant medications
- Vagus Nerve Stimulation (VNS):
  - FDA-approved in 2005 for use in TRD patients who have failed 4+ trials of antidepressant medications
- Cognitive behavioral therapy/Interpersonal therapy (CBT/IPT)
  - Psychotherapeutic techniques with an evidence base in TRD

Evidence Quality

- Most available RCTs were small, single-center studies of poor or fair quality
- Issues with design and methods in many studies:
  - No standardized entry criteria or definitions of TRD employed
  - No assessment of outcomes beyond 1-2 weeks after cessation of treatment
  - Variability in treatment approach and concomitant therapies allowed
  - Frequent unblinding of patients and assessors of outcomes
  - Variation in measures and definitions of response to treatment

Results: Effectiveness*

ECT

- ECT vs. pharmacotherapy (1 RCT): Outcomes favored ECT
- ECT vs. sham (2 RCTs):
  - From 1980s, response/remission not measured
  - Change in depressive severity favored ECT
- ECT vs. rTMS (4 RCTs):
  - Baseline severity similar to other rTMS studies
  - Outcomes favored ECT in 2; no differences in 2
- ECT + rTMS vs. ECT (2 RCTs): No significant differences reported

*Change in depressive severity, response, remission

Results: Effectiveness*

rTMS

- rTMS vs. sham (**24** RCTs):
  - Meta-analyses of Tier 1-2 data suggest rTMS 2-4 times more likely to evoke response/remission
- Key rTMS studies:
  - O'Reardon, 2007→rTMS superior to sham at 4 weeks in subgroup with 1 failed drug trial
    - Largest (n=325) multicenter study available
    - Differences in baseline symptom severity
    - Partial unblinding of study subjects
    - No blinded outcome assessment post-treatment

*Change in depressive severity, response, remission

Results: Effectiveness*

rTMS (cont'd)

- George, 2010→Remission rates significantly higher for rTMS after 3 weeks of treatment (14% vs. 5%, p=.02)
  - Large, NIMH-sponsored multicenter trial (n=190)
  - Additional techniques to ensure blinding
- Mogg, 2008→No significant differences observed at end of treatment (2 weeks), 6 weeks, or 4 months
  - Study design regarded as strong (but not in AHRQ review)
  - Small trial (n=59) with unblinding concerns

*Change in depressive severity, response, remission

Results: Effectiveness*

VNS

- VNS vs. sham (1 RCT):
  - No significant differences reported
  - FDA approval based on observational data alone:
    - FDA review team asked for 2nd RCT
    - Company cited concerns with ethics of surgical, sham-controlled RCT
    - Review team recommended non-approval; overruled by CDRH head

*Change in depressive severity, response, remission

Results: Effectiveness*

CBT/IPT

- CBT vs. pharmacotherapy (2 RCTs):
  - No significant differences reported
- CBT/IPT vs. usual care (4 RCTs):
  - Outcomes favored CBT/IPT in 2; no differences in 2

*Change in depressive severity, response, remission

Results: Maintenance of Remission

- No significant differences reported in any direct or indirect comparisons of ECT, rTMS, or VNS
- CBT/IPT (1 RCT):
  - Significantly lower risk of symptom relapse at 17 months of follow-up vs. usual care (psychiatrist visits and medications): 29% vs. 47%

Results: Other Findings

- Insufficient data to evaluate effectiveness in specific symptom subtypes
- Limited subpopulation data (2 RCTs) suggests rTMS better than sham in young adults and those with post-stroke depression
- Insufficient data to evaluate impact on quality of life

Results: Major Harms

- Cognitive function
  - Head-to-head (3 RCTs, 2 cohort studies): Better function for rTMS vs. ECT in 1, no differences in 4
  - rTMS vs. sham (5 RCTs): Better function for rTMS in 1, no differences in 4
  - ECT vs. sham: Cognitive function not tested
- Specific adverse events
  - Few studies reported specific events
  - Most reported AEs mild and transient (pain, sleep disturbances, headache)
  - No significant differences in study withdrawals due to AEs

NEW EVIDENCE FOLLOWING AHRQ REVIEW

New Evidence

- Search conducted 1/2010 – 10/2011
- 10 studies identified that met AHRQ review entry criteria→no RCTs
- Small observational study of rTMS showing improvement in QoL from baseline—no comparator
- Small safety study documenting increased QTc interval in ECT patients (within normal limits)

CLINICAL GUIDELINES/ COVERAGE POLICIES

Guidelines (APA, VA, NICE)

- ECT: typically recommended for severe MDD, patients with catatonic/psychotic features, & those at high risk of suicide
- rTMS: option for MDD patients with inadequate response to pharmacotherapy
- VNS: option for patients not responding to at least 4 trials of pharmacotherapy and/or ECT
- CBT/IPT: recommended as initial therapy for mild-moderate MDD, as adjunct to pharmacotherapy in moderate-severe MDD, and as alternative to drugs in TRD

Coverage Policies

- ECT: covered by Medicare and private payers for TRD as well as high-risk and emergency situations
- rTMS:
  - Medicare: no NCD; not covered for depression in available LCDs
  - Private payers: not covered
- VNS:
  - Medicare: non-coverage NCD for depression
  - Private payers: not covered for depression
- CBT/IPT: no published policies available; assume coverage subject to limitations in individual benefit packages

NCD: National coverage decision; LCD: Local coverage determination

rTMS Systematic Reviews

- Short-term benefits of rTMS acknowledged in reviews conducted by BCBSTEC, CTAF, and Ontario Ministry of Health
  - Most evidence generated in patients with mild-moderate TRD or 1 failed drug trial
  - Lack of data on clinical significance and durability of effects seen during treatment
  - High variability in rTMS coil placement, intensity, frequency, duration, and use of concomitant drug therapy
- Data felt to be insufficient to determine whether rTMS better than additional trials of drug therapy

BCBSTEC: Blue Cross Blue Shied Technology Evaluation Center; CTAF: California Technology Assessment Forum

BUDGETARY IMPACT ANALYSES

Details

- Estimated for Medicaid and 3 largest private payers in each state
- Assumed prevalence of TRD (literature-based):
  - Private payers: 2.0%
  - Medicaid: 3.4%
  - Corresponds to ~170,000 individuals in NE
- No available data on “mix” of nonpharmacologic interventions for TRD

Resource Utilization

- Baseline resource utilization derived using Northeast norms from IMS LifeLink database:
  - Large (~80 million lives), national database of integrated pharmacy and medical claims from private insurers
  - Includes all utilization in a population with depression
  - Utilization rates inflated to reflect likely consumption in a TRD population (Ivanova, 2010)
  - Reduced use of inpatient/ED services assumed for patients with a treatment response

Payments

- All payments estimated based on median values from IMS database
- ECT: ~$430 per session, ~$3,500 per course (8 sessions)
- rTMS: ~$250 for planning session, ~$200 per session, ~$4,400 per course (20 sessions)
- Payments for other services estimated based on median per-visit rates from IMS database
- Medicaid payments assumed to be 60% of private-pay rates

Scenarios

- Budget impact scenarios focused on potential introduction of coverage for rTMS:
  - Baseline: 20% of TRD patients receiving ECT, 80% "usual care"
  - Scenario 1: 10% ECT, 10% rTMS
  - Scenario 2: 20% ECT, additional 10% receive rTMS
- Response rates for rTMS, ECT, and usual care obtained from AHRQ review:
  - rTMS and ECT assumed to be equivalent: 59%
  - Usual care: 27%

One-Year Budgetary Impact: Medicaid and Private-Pay Populations

Estimate	Baseline	Scenario 1	Net Δ	Scenario 2	Net Δ
Payments per TRD Patient					
ECT and/or rTMS	$668	$781	**$113**	$1,115	**$447**
Outpatient/Meds/ED	$7,767	$7,767	**$0**	$7,718	**($49)**
Inpatient	$1,666	$1,666	**$0**	$1,586	**($80)**
Total	$10,101	$10,214	**$113**	$10,419	**$318**
			1.1%		**3.1%**
Overall Population Impact					
Total Payments	$27,013,330,265	$27,032,402,940	**$19,072,676**	$27,066,896,545	**$53,566,280**
Payments PMPM	$295.68	$295.89	**$0.21**	$296.27	**$0.59**
			0.1%		**0.2%**

Budgetary Impact: Medicaid Only

- Scenario 1 (ECT 10/rTMS 10):
  - Increase of $172 per TRD patient (2.6%)
  - Additional $6.8 million in expenditures region wide
  - PMPM increase from $189.00 to $189.48
- Scenario 2 (ECT 20/rTMS 10):
  - Increase of $308 per TRD patient (4.6%)
  - Additional $12.1 million in expenditures
  - PMPM increase from $189.00 to $189.87

COST-EFFECTIVENESS ANALYSES

Cost-Effectiveness Model

- Economic model focused on outcomes and costs of rTMS and usual psychiatric care in 1,000 hypothetical patients:
  - Only comparison in AHRQ review with any evidence of incremental clinical benefit
- 5-year time horizon selected to reflect balance between short-term budgetary considerations and lifetime outcomes
- Initial treatment response, remission, and relapse of symptoms evaluated in 6-month cycles

Key Assumptions

- As in budgetary impact model, response associated with reduced use of inpatient and ED services
- Patients who relapse return to original (i.e., higher) levels of inpatient and ED use
- 50% of rTMS patients who relapse assumed to retry; all usual care patients continue with usual care
- Quality of life (utility) improves with response and remission, declines with relapse

Key Model Outcomes: rTMS vs. Usual Care

- Based on discounted* direct medical costs

Measure (per patient with TRD)	Usual Care	rTMS	Difference (rTMS-Usual Care)
Life years	4.85	4.85	**0.00**
QALYs	3.62	3.64	**0.02**
Treatment responses	2.63	3.00	**0.37**
Total costs	$31,296	$35,550	**$4,253**
Cost-effectiveness			
Cost per QALY gained			**$216,468**
Cost per add'l treatment response			**$11,803**

*Using 3.5% annual discount rate

Additional Analyses

- Threshold analyses conducted on cost for each rTMS session:
  - Baseline estimate: $206 per session
  - Cost to achieve cost-effectiveness ratio of $100,000 per QALY: $104 per session
  - Cost to achieve cost neutrality for rTMS vs. usual care: $16 per session

QUESTIONS FOR DELIBERATION

Comparative Clinical Effectiveness: rTMS vs. usual care

For patients who have TRD, is the evidence adequate to demonstrate that rTMS provides a net health benefit *equivalent* or *superior* to usual care (i.e., general supportive psychotherapy with or without continued use of antidepressant medication)?

a. If yes:

- Is rTMS *equivalent* or *superior* to usual care?
- Are there criteria for patient selection, provider training, and optimal treatment duration that should be considered?

b. If no, is this due to:

- Inadequate evidence with which to judge comparative net health benefit
- Adequate evidence of an *inferior* net health benefit

Comparative Clinical Effectiveness: rTMS vs. ECT

For patients who have TRD, is the evidence adequate to demonstrate that rTMS provides a net health benefit *equivalent* or *superior* to electroconvulsive therapy (ECT)?

a. If yes:

- Is rTMS *equivalent* or *superior* to ECT?
- Are there criteria for patient selection, provider training, and optimal treatment duration that should be considered?

b. If no, is this due to:

- Inadequate evidence with which to judge comparative net health benefit
- Adequate evidence of an *inferior* net health benefit

Comparative Clinical Effectiveness: ECT vs. usual care

For patients who have TRD, is the evidence adequate to demonstrate that ECT provides a net health benefit *equivalent* or *superior* to usual care (i.e., general supportive psychotherapy with or without continued use of antidepressant medication)?

a. If yes:

- Is ECT *equivalent* or *superior* to usual care?
- Are there criteria for patient selection, provider training, and optimal treatment duration that should be considered?

b. If no, is this due to:

- Inadequate evidence with which to judge comparative net health benefit
- Adequate evidence of an *inferior* net health benefit

Comparative Clinical Effectiveness: VNS vs. usual care

For patients who have TRD, is the evidence adequate to demonstrate that VNS provides a net health benefit *equivalent* or *superior* to usual care (i.e., general supportive psychotherapy with or without continued use of antidepressant medication)?

a. If yes:

- Is VNS *equivalent* or *superior* to usual care?
- Are there criteria for patient selection, provider training, and optimal treatment duration that should be considered?

b. If no, is this due to:

- Inadequate evidence with which to judge comparative net health benefit
- Adequate evidence of an *inferior* net health benefit

Comparative Clinical Effectiveness: CBT/IPT vs. usual care

For patients who have TRD, is the evidence adequate to demonstrate that CBT/IPT provides a net health benefit *equivalent* or *superior* to usual care (i.e., general supportive psychotherapy with or without continued use of antidepressant medication)?

a. If yes:

- Is CBT/IPT *equivalent* or *superior* to usual care?
- Are there criteria for patient selection, provider training, and optimal treatment duration that should be considered?

b. If no, is this due to:

- Inadequate evidence with which to judge comparative net health benefit
- Adequate evidence of an *inferior* net health benefit

Comparative Value: rTMS

Based on reimbursement levels provided with this report, would you judge the comparative value of rTMS to be: 1) high value; 2) reasonable value; or 3) low value for the following comparisons?

1. *rTMS vs. usual care?*
   Please complete the MCDA scoring sheet prior to voting

2. *rTMS vs. ECT?*
   Please complete the MCDA scoring sheet prior to voting

Possible Factors in Your Judgment of "Comparative Value"	Rating from none to big (0-5) or from lowest to highest (0-5) of each factor for this intervention	Rating of *how important* this factor was in your overall judgment of comparative value
Magnitude of the net clinical benefit compared with other available options	0 1 2 3 4 5	0 1 2 3 4 5
Confidence in the evidence on comparative clinical benefit	0 1 2 3 4 5	0 1 2 3 4 5
Magnitude of improvement in safety and tolerability	0 1 2 3 4 5	0 1 2 3 4 5
Confidence in the evidence on improvement of safety and tolerability	0 1 2 3 4 5	0 1 2 3 4 5
Magnitude of the incremental cost-effectiveness ratio (ICER)	0 1 2 3 4 5 (note: the lowest ICER = highest value, so 0 = highest value)	0 1 2 3 4 5
Confidence in the accuracy of the ICER	0 1 2 3 4 5	0 1 2 3 4 5
Budget impact/opportunity cost (other potential uses for $$)	0 1 2 3 4 5	0 1 2 3 4 5
Other reasonable treatment options are available	0 1 2 3 4 5	0 1 2 3 4 5
Severity of the condition	0 1 2 3 4 5	0 1 2 3 4 5
Ability of the intervention to address healthcare disparities	0 1 2 3 4 5	0 1 2 3 4 5
Support for the intervention from clinicians	0 1 2 3 4 5	0 1 2 3 4 5
Special (vulnerable) population	0 1 2 3 4 5	0 1 2 3 4 5
Risk of overuse or misuse	0 1 2 3 4 5	0 1 2 3 4 5
Other:	0 1 2 3 4 5	0 1 2 3 4 5
Other:	0 1 2 3 4 5	0 1 2 3 4 5

Other Considerations

Are there any considerations related to public health, equity, disparities in access or outcomes for specific patient populations, or other social values that should be considered in medical policies related to the use of rTMS, ECT, VNS, or CBT/IPT?

ROUNDTABLE DISCUSSION

Closing

- Further public comments accepted until COB December 21, 2011
- Dissemination plans
- Next meeting: June 2012
- Next topic: To be posted by January 30, 2012