Relapse-prevention with injection naltrexone: patient selection and treatment initiation

Adam Bisaga M.D.
Professor of Psychiatry at CUMC
Columbia University College of Physicians and Surgeons, New York, NY
Outline

• Treatment of Opioid Use Disorder (OUD) with naltrexone
• Selection of patients: individualized treatment
• Treatment initiation scenarios
• Detoxification and naltrexone induction protocols
• MAT Treatment Algorithm
Treatment of OUD with Naltrexone
OUD: Treatment Goals

- **A range of treatment goals**
  - Minimization of harms from ongoing use
  - Sustained recovery with abstinence from all substances and quality of life improvement

- **Medically oriented treatment**
  - Cessation of illicit opioid use
  - Protection against risk of OD and death
  - Improvement in physical and psychological health
  - No dependence on other substances
  - No misuse/diversion of medications

- **Behaviorally oriented treatment**
  - Teaching skills necessary to cope with cravings and life stressors without drugs
  - Helping patients become responsible for the management of their disorder
Antagonist-based Treatment

• Opioid antagonist attach to the receptor and block other opioids from exerting any effects

• Naltrexone is a long-acting, high affinity, competitive opioid receptor antagonist with an active metabolite (6βN)
  • At sufficient blood levels naltrexone fully blocks all opioid effects

• Naltrexone tablet was approved in 1984 for the blockade of exogenously administered opioids

• Naltrexone injection (extended release, Vivitrol) was approved in 2010 for prevention of relapse following opioid detoxification
Naltrexone Treatment: mechanism

- **Behavioral component**: blockade of the positive (reinforcing) effects of heroin leads to gradual extinction of drug seeking
  - Patients who use while on naltrexone experience no effect and stop using
- **Pharmacological component**: naltrexone decreases reactivity to drug-conditioned cues and decreases craving thereby minimizing pathological responses contributing to relapse
  - Patients on naltrexone have decreased urges to use
Naltrexone Treatment: Efficacy

- Treatment retention is significantly better in patients treated with XR-injection as compared oral tablet
- Among patients started on XR-naltrexone, approximately 50-60% are retained in treatment at 6 months and 55-68% at 2-3 months
- Patients treated with naltrexone injection, as compared to placebo, have:
  - Better treatment retention
  - Less opioid use
  - Lower craving for opioids
- Majority of patients retained in treatment with XR-naltrexone have low levels of concurrent opioid use (10-20%)

(Comer et al., 2006, Krupitsky et al., 2011, Bisaga et al. et al., 2014, 2015)
Antagonist-based Treatment: limitations

- Requirement of detoxification and a wait-period of 7-10 days after the last dose of an opioid before treatment can be initiated
  - A major barrier for many patients who find difficult to tolerate withdrawal
  - Further complicated by the reduction of inpatient/residential treatment programs
- Difficulty with the induction due to the possibility of precipitated or protracted withdrawal
  - Patients do not feel well at the beginning of the treatment
  - Requirement of close monitoring
- XR preparation of naltrexone is a relatively new medication with limited effectiveness research to date
  - No direct evidence yet available comparing efficacy of XR-naltrexone vs. agonists
## Choosing Agonist vs. Antagonist Based Treatment

<table>
<thead>
<tr>
<th></th>
<th>AGONIST</th>
<th>ANTAGONIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain physiological dependence with withdrawal on stopping</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Reinforcing effects promoting medication adherence</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Euphoric effects with a potential for abuse and diversion</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Eliminates ongoing illicit opioid use</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Protection against overdose during treatment</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risk of overdose after treatment dropout</td>
<td>+</td>
<td>++ (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ (XR)</td>
</tr>
<tr>
<td>Professional and public opposition and barriers to availability</td>
<td>+</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Selection of patients: individualized treatment
Selection of Candidates for Naltrexone

• Patients who are not interested or able to be on agonist maintenance
  ▪ Highly motivated for abstinence from all opioids (e.g., active in 12-step programs)
  ▪ In professions where treatment with agonist is still controversial (e.g., healthcare professionals, pilots)

• Patients who are detoxified and abstinent but at risk for relapse
  ▪ Released from a controlled setting (prison, residential program)
  ▪ Moving back to old neighborhood,
  ▪ With increased stress or worsening of psychiatric problems
Selection of Candidates for Naltrexone (2)

- Patients who failed prior treatment with agonist
  - Continued to have cravings and used of opioids, non-compliant with agonists, diverting/misusing agonists, dropped out of treatment

- Patients with less severe form of a disorder
  - Short history of use, lower level of use

- Young adults which often unwilling to commit to a long-term agonist maintenance

- Individuals who use opioids sporadically

- Patients successful on agonist but who want to discontinue them without risking relapse
Patients who may have good response to treatment with naltrexone

• Highly motivated patients who are committed to abstinence and engaged in recovery work
• Older patients with long history of use and multiple relapses
• Young adults living with involved parents who supervise treatment
• Patients with long periods of abstinence between relapses
Patients who may be better candidates for agonists

- Patients with history of overdoses, particularly following detoxification
- Patients with limited social supports (unstable lives, homeless)
- Patients who have been opiate-free but never felt “normal”
  - Patients in whom psychiatric illness emerged/worsened after previous detoxifications (with or w/o naltrexone)
- Patients with chronic pain requiring chronic opioid treatment
Patients who may be better candidates for agonists (2)

- Patients with severe GI disorders exacerbating during withdrawal/abstinence
- Patients with advanced liver disease
  - Concerns about hepatotoxicity were not based on the representative data and the black-box warning was removed from the medication label
    - Patients with LFT’s less than 3-5 times upper normal limit have minimal risk
Treatment initiation scenarios
Type of naltrexone candidates

- Detoxified and abstinent (e.g., patients leaving controlled setting: residential treatment, prison)
- Using opioids sporadically
- Using daily, low-doses of opioids
- Using daily large amounts of short acting agents (heroin)
- Using large amounts of long-acting agents (XR oxycodone, fentanyl, methadone)
- Patients maintained on methadone or buprenorphine
Detoxified and Abstinent

• Individuals who are detoxified and abstinent but at risk for relapse are the easiest cases to induce onto XR-NTX
  ▪ Released from a controlled setting (prison, residential program)
  ▪ Detoxified as outpatients and have not used any opioids for at least 7 days, not in acute withdrawal
  ▪ Abstinent for some time but at increased risk of relapse

• Confirmed absence of opioids and physical dependence
  • Urine drug screen negative for all opioids (opiates, oxycontin, buprenorphine, methadone, fentanyl)
  • Negative naloxone challenge (if unsure)
  • Understands the risks of precipitated w/d if underreporting

• Administer injection of XR-NTX
  • May give one test dose of oral naltrexone (25 mg/d) 2-4 hours prior to injection to make sure that the patient tolerates naltrexone
Using opioids sporadically

• Individuals who started using after a period of abstinence

• High-risk intermittent users of opioids (with/without other substances)

• Require abstinence from opioids (2-3 days) and confirm absence of physical dependence
  - Urine drug screen negative for all opioids (opiates, oxycontin, buprenorphine, methadone, fentanyl)
  - Negative naloxone challenge
  - Understands the risks of precipitated w/d if underreporting

• Administer test doses of oral naltrexone for 1-2 days (low-dose e.g., 12.5 mg, 25 mg)

• If oral naltrexone is tolerated, administer XR-NTX injection
  - Need to wait at least 60 min after oral challenge before injection
Using daily, low amounts

- Patients who misuse opioids in the context of pain-treatment (<100 mg morphine equivalents)
- Individuals using low amounts of heroin (1-3 bags/day)
- Require detoxification that can be done on outpatient basis (daily visits for monitoring and medications)
  - Agonist-assisted
  - Antagonist-assisted
  - Symptomatic-only treatment
- Confirm absence of physical dependence
  - Negative toxicology and negative naloxone challenge
- Administer test doses of oral naltrexone for 1-2 days (low-dose e.g., 12.5 mg, 25 mg)
- If oral naltrexone is tolerated, administer XR-NTX injection
Using daily, large amounts

- Individuals using large amounts of short or long-acting opioids, often IV (>5 bags heroin, >100 mg mor, oxy, fentanyl, regular methadone)
- Often using other substances (psychostimulants, alcohol, sedatives)
- Consider stabilization/maintenance on agonist as a first-line treatment
- If wishes to be treated with naltrexone consider inpatient detoxification (10-14 days)
  - Agonist-assisted
  - Antagonist-assisted
- Confirm absence of physical dependence with naloxone challenge or administer test dose of oral naltrexone (12.5-25 mg) followed by XR-NTX injection if tolerated
- Administer naltrexone injection before discharge
Maintained on agonist

• Individuals maintained on methadone and buprenorphine with good response may be considered for transition onto naltrexone

• Patients should be able to tolerate gradual agonist dose reduction
  • Patients maintained on methadone should be transitioned onto buprenorphine
  • All patients should remain stable on buprenorphine 2-4 mg for at least 1 month before discontinuation

• Adjunctive medications may be used after buprenorphine discontinuation

• Initiate treatment with oral naltrexone
  • May wait for urine buprenorphine screen to become negative

• Administer test dose of oral naltrexone (12.5-25 mg) followed by XR-NTX injection
Naloxone challenge

- Naloxone is a short-acting opioid antagonist used to reverse overdose and to detect physiological dependence
- In dependent individuals, naloxone will precipitate withdrawal that usually emerges within 5-10 min and dissipates within 30 min (naloxone challenge or Wang Test)
  - Can be measured using standard instruments (e.g., COWS)
  - Severity of withdrawal is proportional to the level of physical dependence
  - Any change from baseline, particularly appearance of objective signs, evidences positive test
- Naloxone is given IM 0.8-1.2 mg (2-3 cc)
  - To minimize risk of significant WD, may administer in 2 stages, 0.4 mg followed by 0.8 mg
- With the negative test, full dose naltrexone can be started
  - Naltrexone should not be given after the positive test (it will precipitate withdrawal lasting many hours), in that case naloxone challenge can be repeated the next day
Measuring Opioid Withdrawal

Several scales are available, objective, subjective or mixed

<table>
<thead>
<tr>
<th>Clinical Opiate Withdrawal Scale (COWS)</th>
<th>Objective Opiate Withdrawal Scale (OOWS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.</td>
<td>Yawning</td>
</tr>
<tr>
<td>Patient's Name: ______________________ Date and Time <strong>/</strong>/<strong><strong>:</strong></strong>:____</td>
<td>1 ≥ 1 yawn</td>
</tr>
<tr>
<td>Reason for this assessment: ______________________</td>
<td>Rhinorrhea</td>
</tr>
<tr>
<td>Restina Pulse Rate: ________ beats/minute</td>
<td>1 ≥ 3 sniffs</td>
</tr>
<tr>
<td>Measured after patient is sitting or lying for one minute</td>
<td>Piloerection (observe arm)</td>
</tr>
<tr>
<td>0 pulse rate 80 or below</td>
<td>1 = present</td>
</tr>
<tr>
<td>1 pulse rate 81-100</td>
<td>Perspiration</td>
</tr>
<tr>
<td>2 pulse rate 101-120</td>
<td>1 = present</td>
</tr>
<tr>
<td>4 pulse rate greater than 120</td>
<td>Lacrimation</td>
</tr>
<tr>
<td>Sweating: over past ½ hour not accounted for by room temperature or patient activity.</td>
<td>1 = present</td>
</tr>
<tr>
<td>0 no report of chills or flushing</td>
<td>Tremor (hands)</td>
</tr>
<tr>
<td>1 subjective report of chills or flushing</td>
<td>1 = present</td>
</tr>
<tr>
<td>2 flushed or observable moistness on face</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>3 beads of sweat on brow or face</td>
<td>1 ≥ 3 mm</td>
</tr>
<tr>
<td>4 sweat streaming off face</td>
<td>Hot and cold flushes</td>
</tr>
<tr>
<td>Restlessness Observation during assessment.</td>
<td>1 = shivering/huddling</td>
</tr>
<tr>
<td>0 able to sit still</td>
<td>Restlessness</td>
</tr>
<tr>
<td>1 reports difficulty sitting still, but is able to do so</td>
<td>1 = present</td>
</tr>
<tr>
<td>3 frequent shifting or extraneous movements of legs/arms</td>
<td>Anxiety</td>
</tr>
<tr>
<td>5 Unable to sit still for more than a few seconds</td>
<td>1 ≥ 3 mm</td>
</tr>
<tr>
<td>Pupil size</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>0 pupils pinned or normal size for room light</td>
<td>1 ≥ 3 mm</td>
</tr>
<tr>
<td>1 pupils possibly larger than normal for room light</td>
<td>Hot and cold flushes</td>
</tr>
<tr>
<td>2 pupils moderately dilated</td>
<td>1 = shivering/huddling</td>
</tr>
<tr>
<td>5 pupils so dilated that only the rim of the iris is visible</td>
<td>Restlessness</td>
</tr>
<tr>
<td>Bone or Joint aches If patient was having pain previously, only the additional component</td>
<td>1 = present</td>
</tr>
<tr>
<td>attributed to opiate withdrawal is scored</td>
<td>Vomiting</td>
</tr>
<tr>
<td>0 not present</td>
<td>1 frequent shifts</td>
</tr>
<tr>
<td>1 mild diffuse discomfort</td>
<td>Muscle twitches</td>
</tr>
<tr>
<td>2 patient reports severe diffuse aching of joints/ muscles</td>
<td>1 = present</td>
</tr>
<tr>
<td>4 patient is rubbing joints or muscles and is unable to sit still because of discomfort</td>
<td>Abdominal cramps</td>
</tr>
<tr>
<td>Runny nose or tearing Not accounted for by cold symptoms or allergies</td>
<td>1 = holding stomach</td>
</tr>
<tr>
<td>0 not present</td>
<td>Anxiety</td>
</tr>
<tr>
<td>1 nasal stuffiness or unusually moist eyes</td>
<td>1 mild - severe</td>
</tr>
<tr>
<td>2 nose running or tearing</td>
<td></td>
</tr>
<tr>
<td>4 nose constantly running or tears streaming down cheeks</td>
<td></td>
</tr>
<tr>
<td>Total Score ________</td>
<td>The total score is the sum of all 11 items</td>
</tr>
<tr>
<td>The initial score is the sum of all 11 items</td>
<td>Initials of person</td>
</tr>
<tr>
<td>completing Assessment: ______________________</td>
<td></td>
</tr>
</tbody>
</table>

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal
Source: Wesson and Ling 2003

**Objective Opiate Withdrawal Scale (OOWS)**

| Yawning | 0 = no yawns |
| 1 ≥ 1 yawn |
| Rhinorrhea | 0 = < 3 sniffs |
| 1 ≥ 3 sniffs |
| Piloerection (observe arm) | 0 = absent |
| 1 = present |
| Perspiration | 0 = absent |
| 1 = present |
| Lacrimation | 0 = absent |
| 1 = present |
| Tremor (hands) | 0 = absent |
| 1 = present |
| Mydriasis | 0 = absent |
| 1 ≥ 3 mm |
| Hot and cold flushes | 0 = absent |
| 1 = shivering/huddling |
| Restlessness | 0 = absent |
| 1 = present |
| Vomiting | 0 = absent |
| 1 frequent shifts |
| Muscle twitches | 0 = absent |
| 1 = present |
| Abdominal cramps | 0 = absent |
| 1 = holding stomach |
| Anxiety | 0 = absent |
| 1 mild - severe |
Detoxification and naltrexone induction protocols
Detoxification

- Naltrexone is an opioid receptor antagonist and can only be started in individuals who are detoxified.
- When naltrexone is given to patients who are physically dependent (and have heroin in their system) naltrexone will displace heroin off the receptor and precipitate withdrawal symptoms within:
  - As opposed to a slow onset of a spontaneous withdrawal
  - Precipitated withdrawal may present with atypical signs (e.g. delirium)
- Even if there is no agonist in the system (e.g., 48 hrs after the last heroin dose) patients are still physically dependent and naltrexone, especially in higher doses, will precipitate withdrawal.
Main Detoxification Approaches

- Agonist-assisted detoxification
- Symptomatic-only treatment
- Rapid detoxification using antagonist
- Ultra-Rapid detoxification under anesthesia
Initiating Naltrexone

- Two phases of treatment: 1) detoxification, 2) naltrexone induction
- Current FDA-sanctioned method involves 7-10 days “washout” period between the two phases: last dose of opioid and first dose of NTX

**Detoxification**
- agonist-assisted + opioid washout
- symptomatic only

**NTX Induction**
- Not using agonist during detox, shortens duration of “washout”
- Introducing naltrexone during detoxification accelerates the process of induction
Naltrexone Initiation During Detoxification: Rapid Naltrexone Induction Procedure

- Protocol may be modified depending on the level of physiological dependence
- Low starting doses of naltrexone (1-3 mg) will minimize precipitated withdrawal while accelerating time to the full dose
- Approximately 70% of patients complete inpatient and 60% complete outpatient procedure and accept naltrexone injection

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buprenorphine</strong></td>
<td>admission</td>
<td>4 mg bid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Naltrexone</strong></td>
<td></td>
<td></td>
<td>3 mg</td>
<td>6 mg</td>
<td>25 mg</td>
<td>50 mg po</td>
<td>380 mg im</td>
</tr>
<tr>
<td><strong>Supportive medications</strong></td>
<td>clonidine 0.1-0.2 mg qid, clonazepam 0.5-1.0 mg tid, prochlorperazine, zolpidem, trazodone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Transition from Buprenorphine Maintenance to Naltrexone

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buprenorphine</strong></td>
<td>2 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Naltrexone</strong></td>
<td></td>
<td>1-3 mg</td>
<td>6 mg</td>
<td>25 mg</td>
<td>50 mg</td>
<td>380 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Supportive</strong></td>
<td>clonidine 0.1-0.2 mg qid, clonazepam 0.5-1.0 mg tid, Prochloperazine, zolpidem, trazodone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Many people who are unable to taper off buprenorphine may have a greater sensitivity to withdrawal symptoms or an anxiety disorder both of which can benefit from ancillary medications and support.
- Some of patients who stop buprenorphine maintenance experience protracted withdrawal (anxiety, low energy, or amotivation) that may benefit from symptomatic treatment.
<table>
<thead>
<tr>
<th>Withdrawal Symptoms</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autonomic arousal (sympathetic)</strong></td>
<td>$\alpha_2$-Adrenergic agonists</td>
</tr>
<tr>
<td><strong>Anxiety/restlessness</strong></td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td>Sedating antidepressants</td>
</tr>
<tr>
<td></td>
<td>Non-benzodiazepine hypnotics</td>
</tr>
<tr>
<td></td>
<td>Sedating atypical neuroleptics</td>
</tr>
<tr>
<td><strong>Musculo-skeletal pain</strong></td>
<td>NSAIDs</td>
</tr>
<tr>
<td></td>
<td>Aniline analgesics (acetaminophen)</td>
</tr>
<tr>
<td><strong>GI Distress (nausea, vomiting, diarrhea)</strong></td>
<td>Oral hydration</td>
</tr>
<tr>
<td></td>
<td>Antiemetics</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
</tr>
</tbody>
</table>
Protracted Withdrawal: Naltrexone Flu

• Patients who start naltrexone right after detoxification commonly experience a “flu-like” symptoms (low-grade withdrawal)
  ▪ Somatic complaints: insomnia, GI distress, hyperalgesia, anergia
  ▪ Anxiety, irritability, dysphoria, anhedonia
  ▪ Symptom severity correlated with naltrexone dose and timing
  ▪ Severity may be lower if naltrexone initiation is postponed (but relapse risk)

• Partially alleviated with aggressive symptomatic treatment,
  ▪ Insomnia (v. frequent, often severe): zolpidem, trazodone, quetiapine
  ▪ GI distress: H2 blockers
  ▪ Anxiety/hyperarousal: clonazepam, clonidine, gabapentin

• Most of these symptoms remit by 2-4 weeks
  ▪ True prolonged symptoms are rare and likely reflect additional psychopathology
Opioid Dependent Patients who are NOT Physically Dependent

Returning to High Risk Environment
- Increased stress
- Persistent Craving

- YES
  - Relapse Prevention CBT
  - Support Groups

- NO
  - Relapse Prevention CBT
  - Support Groups
  - NALTREXONE P.O.
  - PRN

- YES
  - NALTREXONE XR
  - Relapse Prevention CBT
  - Support Groups
Patients who are actively using

- Educate About Treatment Options
- Assess Patient’s Preference
- Assess Prognostic Factors
- Determine First-Line Treatment

Abstinence Induction Using AGONIST

- METHADONE STABILIZATION
- BUPRENORPHINE STABILIZATION

- Response
  - Yes: METHADONE MAINTENANCE
  - No: BUPRENORPHINE MAINTENANCE

Detoxification and Relapse Prevention Using ANTAGONIST

- NALTREXONE XR STABILIZATION

- Response
  - Yes: NALTREXONE XR MAINTENANCE
  - No: Response

Patients who are actively using

- Abstinence Induction Using AGONIST
- NALTREXONE XR STABILIZATION
- BUPRENORPHINE MAINTENANCE
Providers’ Clinical Support System
For Medication Assisted Treatment

What We Do
We are a national training and mentoring project developed in response to the prescription opioid misuse epidemic and the availability of newer pharmacotherapies to address opioid use disorder. The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

View Modules
The foundation for provider education on topics related to medication-assisted treatment for opioid use disorder.
Start Training

Find a Mentor
The mentor program provides individualized support and mentoring for providers treating opioid use disorder.
Connect Now

Watch Webinars
Webinars provide expanded education targeted at clinicians engaged in the treatment of opioid-dependent patients.
Watch Now

Calendar of Events
View Full Calendar

What’s New
PCSS-MAT is a collaborative effort led by American Academy of Addiction Psychiatry in partnership with: American Osteopathic Academy of Addiction Medicine, American Psychiatric Association, American Society of Addiction Medicine and Association for Medical Education and Research in Substance Abuse.

For more information visit: www.pcssmat.org
For questions email: pcssmat@aaap.org

Twitter: @PCSSProjects

Funding for this initiative was made possible (in part) by Providers’ Clinical Support System for Medication Assisted Treatment (grant no. 5U79TI024697) from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.