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Pharmacotherapy of Alcohol Use Disorders in 2017:

What is the First Line Medication?

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Objectives

- Following this presentation, participants should be able to:
  - Name the 4 FDA-approved medications and 1 other efficacious medication for AUD
  - Identify adverse effects, major risks, and contraindications of these AUD medications
  - Name which AUD medications can be used with which specific AUD patient populations

Case Example

- Your 57 yo male patient tells you he is drinking heavily and wants help
- He is still drinking; has not yet stopped
- He wants to reduce, not stop
- He is on opioid analgesics
- His LFTs are elevated to 3x ULN
- His EGFR/CrCl indicates moderately severe renal fn imapairment

Underutilization of AUD Pharmacotherapy

- Alcohol is one of only 3 substances (others are tobacco and opioids) with FDA-approved efficacious medications available
- And there are also some efficacious *non*-FDA-approved pharmacotherapies
- Yet there is very little use of AUD medications
- Reasons unclear, multiple, may include perception of ineffectiveness
- only 8% of adults in the US with AUD are treated with medications

(SAMHSA. *Results from the 2012 National Survey on Drug Use and Health:* ://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/Index.aspx. Accessed July 15, 2014.

- In several large VA studies over the past decade, very few veterans with AUD were receiving AUD medications
  - 4% of VA patients with AUD received meds in FY 2009

(Harris AH et al. Pharmacotherapy of alcohol use disorders by the Veterans Health Administration: patterns of receipt and persistence. *Psychiatr Serv.* 2012;63(7):679-685).

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AUD Pharmacotherapy: Some Key Issues

- AUD patients are heterogeneous
  - Some medications are contraindicated, absolutely or relatively in certain patient groups (e.g. those taking opioids or with severe liver dz), in certain stages of AUD (e.g active drinking vs remission)
  - Response to any one AUD medication is difficult to predict
    - Genetic factors may play a key role in response
- Different AUD medications present different
  - Effects size differences
  - adverse effect profiles
  - risk/benefit ratios
  - adherence challenges
  - costs

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Alcohol's Neuropharmacologic Effects

Anton et al . 2014 Pharmacologic treatment of alcoholism. Ch 30 in *Handbook of Clinical Neurology*. 125 (3rd Ed) Alcohol and the Nervous System, Sullivan EV & Pfefferbaum A Eds.

- Elevates DA in the NAcc →salient attention, reinforcement, brain reward
- Opioid (Beta-endorphin) release→ DA release in NAcc
- GABAergic effects during intoxication; downregulation after chronic use
- Glutamate upregulation with chronic use, increase during withdrawal
- Other neurochemical effects include
  - nicotinic cholinergic receptors
  - 5-HT
  - NA
  - Cannabinoid
  - Nociceptin-orphanin/ORL

Some Neurochemical Targets for AUD Medications

(***adapted from*** Anton et al . 2014 Pharmacologic treatment of alcoholism. Ch 30 in *Handbook of Clinical Neurology*. 125 (3rd Ed) Alcohol and the Nervous System, Sullivan EV & Pfefferbaum A Eds..)

Phenomenon	Neurochemistry	Pharmacotherapy
Reward	Opioids Glutamate 5-HT3 Nicotinic cholinergic	**Naltrexone*** **Acamprosate*,Topiramate** Ondansetron Varenicline
Protracted withdrawal/dysphoria/ anxiety	Glutamate GABA	**Acamprosate*,Topiramate** Gabapentin, Baclofen
Impulsivity	Glutamate Opioids DA	**?Topiramate** **?Naltrexone**

* = FDA-approved; **Boldface** = more evidence exists for efficacy

Efficacious AUD Pharmacotherapies

- FDA-approved
  - **Disulfiram** (Antabuse)
  - **Acamprosate** (Campral)
  - **Naltrexone**
    - Oral
    - Extended-release intramuscular (Vivitrol)
- Non-FDA-approved
  - **Topiramate** (Topamax, others)
  - Gabapentin (?)
  - Some others:
    - Nalmefene
    - Ondansetron (?)
    - Varenicline (?)
    - Baclofen (?)
    - Pregabalin
    - Zonisamide

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Some Patient Groups with Clinical Relevance

- Abstinent vs nonabstinent
- On opioids vs not on opioids
- Severe liver disease vs no severe liver disease
- Renal impairment vs not
- Goal
  - abstinence vs use reduction ("controlled use")
- Logistical:
  - Access to financial means or to providers with specialized training

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Possible Predictors

- Gender
- Craving
- Family history
- Sweet-liking
- Typology: early vs late onset
- Abstinence vs still using at tx onset
- Adherence capacity

- **Genetic variation** involving alleles for genes coding for opioid, glutamate, and other receptors

Disulfiram, 1

- Oldest: FDA approved in 1949
- Mechanism of action of disulfiram (Antabuse)
  - Chemical: inhibits acetaldehyde dehydrogenase
  - Behavioral: anticipation of aversive consequence of drinking discourages use – alters decisional balance
- Pharmacology
  - Irreversible inhibitor of acetaldehyde dehydrogenase
  - Prevents conversion of acetaldehyde →acetate→CO2+H2O
  - Inhibition can last for days – occasionally up to 14 days
  - Disulfiram-alcohol reaction: headache, flushing, nausea, vomiting, chest pain, vertigo, sweating, weakness, hypotension
- Evidence for efficacy
  - Blinded studies show no benefit over placebo (Jonas 2014; Skinner 2014)
  - Open-label studies show efficacy over control groups (Skinner 2014)
  - Most effective in supervised administration

Disulfiram, 2

- Dose:
  - 250 – 500 mg once per day
  - Controversy about whether dose should be increased if patients drink and do not have DSF/Alcohol reaction ; or whether DSF should be DC'ed
- Adverse effects
  - Drowsiness, headache, metallic/garlic taste, rash, very rarely psychosis
  - Occasional: transaminitis
  - Rare: fulminant hepatotoxicity
- Contraindications:
  - Alcohol use in past 24 hours
  - Severe cardiovascular disease
  - Pregnancy/nursing
- Predictors of efficacy
  - Commitment to abstinence, observed adherence
- Clinical use
  - Can't be used in patients who are still drinking
  - Contraindicated in pregnant/nursing women
  - LFTs before, every 3 months for 6 months, then every 6 months
  - Warn pts about "hidden" alcohol: food, mouthwash, etc.

Acamprosate, 1

- FDA-approved in 2004
- Mechanism of action of acamprosate (Campral)
  - Modulation of glutamatergic hyperactivity following cessation of alcohol use
  - Thought to reduce withdrawal-associated dysphoria
- Pharmacology
  - Short half life requires TID dose
- Dose: 2 tablets 3x/day (total 1998 mg/day)
- Evidence for efficacy
  - 3 European studies led to US FDA approval
  - Meta-analysis shows efficacy in reducing return to any drinking (NNT 12) (Jonas 2014 JAMA)
  - However, not a single US study has shown separation from placebo in ITT analyses (e.g. Project COMBINE failed to show efficacy)

Acamprosate, 2

- Adverse effects
  - Diarrhea, fatigue, insomnia
- Predictors of efficacy
  - Detoxification and abstinence initiation prior to start
  - High motivation for abstinence (as opposed to use reduction or "controlled" drinking)
  - Ability to adhere to complex regimen
  - Possibly: female gender, high anxiety, negative family hx,late age of onset (Franck & Jayaram-Lindsrom 2013)
- Contraindications
  - pregnant/nursing women
  - renal failure
- Clinical use
  - Can be used in patients who are still drinking
  - Reduce dose to 50% in renal impairment (CrCl 30-50); contraindicated CrCl <30
  - Monitor adherence – very difficult 3x/day regimen

Naltrexone, 1

- FDA-approved for AUD: oral in 1994, XR-NTX in 2006
- 2 forms: oral and injectable extended-release naltrexone (XR-NTX) (Vivitrol)
- Mechanism of action
  - Mu-opioid antagonist; thought to reduce effects of alcohol-mediated increase in beta endorphin and subsequent increase in DA in NAc
  - Reduces craving and reduces pleasurable effects of alcohol
  - May improve decision-making, reduce hypersalience of alcohol cues, reduce impulsivity
- Pharmacology
  - Oral: once daily
  - Extended-release - given monthly
- Dose
  - Oral: 50 mg once per day
  - XR-NTX: monthly IM 380 mg
- Evidence for efficacy
  - Oral reduces return to any drinking and return to heavy drinking
  - Injectable reduces heavy drinking days (Jonas 2014)

Naltrexone, 2

- Adverse effects
  - GI upset: nausea, cramping; dizziness, nervousness, fatigue,
  - Occasional transaminitis
  - XR-NTX: injection site reactions; rare – abscess, necrosis
- Contraindications
  - Opioid treatment (within past 7-10 days)
  - pregnant/nursing women
  - Acute hepatitis or liver failure
- Predictors of effectiveness
  - *Positive family history*
  - *Having the G allele for the OPRM1 gene (A to G, or Asn40Asp substitution) does not appear to predict who responds better by greater NTX-mediated blunting of alcohol reward* *(Oslin JAMA Psychiatry 2015)*
  - Early onset AUD ("Type B")
  - High craving
  - "sweet-liking"

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Naltrexone, 3

- Clinical use
  - NTX can be used in patients who are still drinking
  - Monitoring: LFTs before, q3 months for 6 months, then q6months
  - Pain control may require non-opioid approaches
    - NSAIDS, local, regional, conscious sedation
    - NOTE: *see CSAM Webinar on perioperative pain and acute pain management in patients receiving opioid agonists or antagonists*
  - XR-NTX form greatly improves adherence
    - Intragluteal IM

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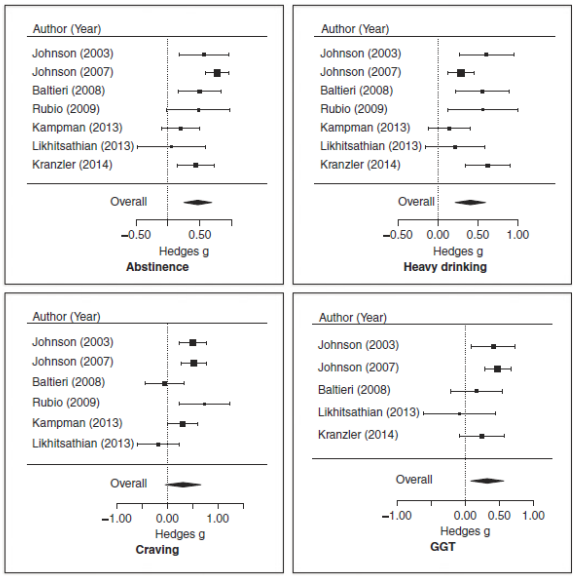
Topiramate, 1

- Not FDA-approved for AUD, but approved as an anticonvulsant and migraine prophylaxis medication
- Mechanism of action of topiramate (Topamax and others)
  - Chemical:
    - Facilitates GABA neurotransmission; inhibits AMPA-kainate glutamate transmission
  - Behavioral
    - May reduce post-withdrawal dysphoria; reduces craving; may reduce impulsivity
- Pharmacology
  - BID dosing
- Dose
  - Precise dose needed is unknown; most studies have used dosing up to 300 mg/day, titrated up slowly from 25 mg/day to 300 mg /day over 6 weeks – increase by 25-50 mg/day each week.
  - Lower doses, eg. 100-200 mg/day may be effective – more research is needed.
  - BID dosing
- Adverse effects
  - Memory and concentration problems; dizziness; somnolence
  - Paresthesias, altered taste
  - Appetite/weight loss
  - Rare: kidney stones, metabolic acidosis, narrow-angle glaucoma

Topiramate, 2: Evidence for Efficacy

(Blodgett et al. 2014 A Meta-analysis of topiramate's effects for individuals with alcohol use disorders. *Alcoholism Clin Exp Research.)*



Forest plots of the effects of topiramate compared with placebo (random-effects models; Hedges *g* and 95% CI).

Topiramate, 3

- Evidence for efficacy: meta-analyses
  - Blodgett (2014) found efficacy greater than NTX or acamprosate , with largest effect for increasing abstinence, and for reducing heavy drinking
  - Jonas (2014) found efficacy for reducing heavy drinking days and drinks per drinking day
- Predictor of effectiveness
  - possible genetic predictor – alleles for GRIK1 gene
- Contraindications
  - Renal failure
  - History of kidney stones or narrow-angle glaucoma
  - pregnant/nursing women
- Clinical use
  - Can be used in patients who are still drinking
  - If CrCl <70 ml/min→cut dose by 50%
  - Check bicarbonate level if metabolic acidosis is suspected (hyperventilation, etc)

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Gabapentin, 1

- Not FDA-approved for AUD, but approved as anticonvulsant; neuropathic pain med
- Mechanism of action of gabapentin (Neurontin and others)
  - Chemical: facilitates GABA transmission
  - Behavioral: reduces withdrawal-related anxiety, helps sleep,
- Pharmacology
  - Blocks alpha-2-delta subunit of calcium channel → modulates GABA neurotransmission
- Dose
  - 1800 mg/day in 3 divided doses
- Evidence for efficacy
  - Mason (2014) JAMA Int Med: increased abstinence, reduced craving
- Adverse effects
  - Sedation, dizziness, edema

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Gabapentin, 2

- Predictors of effectiveness
  - Not clear at this time
- Clinical use
  - Can be used in individuals still drinking
  - Can be used in patients with severe liver disease
  - Evidence exists for GBP aiding sleep in AUD patients
  - Care needs to be taken in cases of renal insufficiency; dose should be reduced

Baclofen

- Not FDA-approved for AUD; approved as muscle relaxant for treating spasticity
- Mechanism of action
  - Chemical: facilitates GABA function
  - Behavioral: may reduce anxiety/dysphoria of post-withdrawal state
- Pharmacology
  - GABAb receptor agonist
- Dose
  - 10-20 mg TID
- Evidence for efficacy: mixed– *mostly negative*
  - Jonas 2014 meta-analysis failed to find efficacy; several European controlled trials support use; 2 recent large controlled US trials failed to show benefit
- Adverse effects
  - Fatigue, sedation, dizziness, abdominal pain; overdose can be dangerous
- Predictors of effectiveness
  - None established
- Clinical use
  - Can be used in patients who are still drinking
  - Renal clearance, so can be used in patients with severe liver disease

Other Possible AUD Pharmacotherapies

- Ondansetron
- Nalmefene
- Varenicline

Case Example, 1

- Your 57 yo male patient tells you he is drinking heavily and wants help

Case Example, 2

- Your 57 yo male patient tells you he is drinking heavily and wants help
- He is still drinking; has not yet stopped

Case Example, 3

- Your 57 yo male patient tells you he is drinking heavily and wants help
- He is still drinking; has not yet stopped
- His goal is to reduce, not stop

Case Example, 4

- Your 57 yo male patient tells you he is drinking heavily and wants help
- He is still drinking; has not yet stopped
- He wants to reduce, not stop
- He is prescribed opioid analgesics

Case Example, 5

- Your 57 yo male patient tells you he is drinking heavily and wants help
- He is still drinking; has not yet stopped
- He wants to reduce, not stop
- He is on opioid analgesics
- His LFTs are elevated to 3x ULN

Case Example, 6

- Your 57 yo male patient tells you he is drinking heavily and wants help
- He is still drinking; has not yet stopped
- He wants to reduce, not stop
- He is on opioid analgesics
- His LFTs are elevated to 3x ULN
- His EGFR/CrCl indicates moderately severe renal fn imapairment

Is There a First Line Medication for AUD?

Probably:

…..oral Naltrexone

- start at 25 mg/day (1/2 tablet) for 2 days, then 50 mg, with food
- check transaminases before and after 3 mos

But Is There Really a First Line Medication for AUD?, 1

- It depends…

Is There a First Line Medication for AUD?, 2

- If abstinent: can use disulfiram
  - Naltrexone oral or XR-NTX
  - Topiramate
  - Acamprosate
  - Disulfiram

Is There a First Line Medication for AUD?, 3

- If still drinking:
  - Can't use disulfiram
  - Choices:
    - Naltrexone oral or XR-NTX
    - Acamprosate
    - Topiramate

Is There a First Line Medication for AUD?, 4

- If using opioids:
  - Can't use Naltrexone oral or XR-NTX
  - Choices:
    - Acamprosate
    - Disulfiram
    - Topiramate

Is There a First Line Medication for AUD?, 5

- If severe liver disease:
  - Disulfiram is risky: occasional transaminitis; rare fulminant liver fl
  - Naltrexone oral or XR-NTX may cause transaminitis
  - Choices:
    - Acamprosate
    - Topiramate
    - Gabapentin

Is There a First Line Medication for AUD?, 6

- If severe renal impairment:
- These are renally cleared → cut dose in half
  - Topiramate
  - Acamprosate
  - Gabapentin
  - Baclofen
- These are hepatically metabolized
  - Naltrexone
  - Disulfiram

Is There a First Line Medication for AUD?, 7

- If female patient of reproductive age and not reliably using birth control, check for pregnancy and check if nursing.
  - If pregnant or nursing:
    - *No current AUD pharmacotherapies are considered safe*

Is There a First Line Medication for AUD?, 7

It depends… perhaps pharmacogenomic data will ultimately inform prescribing

TABLE 1. Brief Review of Positive Findings of Genetic Influences in Alcohol Pharmacotherapy

Medication	Genetic Variant	Outcome Moderated	Notable Studies
Topiramate	*GRIK1* (rs2832407)	Heavy drinking days (%); side effects	Kranzler et al., 2014 (2); Ray et al., 2009 (4)
Naltrexone	*OPRM1* (Asn40Asp), (rs1799971), DRD4 VNTR	Heavy drinking days (%); abstinence rates; relapse to heavy drinking	Anton et al., 2008 (12); Kim et al., 2009 (13); Oslin et al., 2003 (14); Tidey et al., 2008 (15)
Ondansetron	LL/LS/SS (5-HTTLPR) (rs1042173), *SLC6A4* (5-HTTLPR)	Drinks per drinking day; days abstinent (%)	Johnson et al., 2011 (9)
Sertraline	5-HTTLPR triallelic *SLC6A4*	Heavy drinking days (%); drinking days (%)	Kranzler et al., 2011 (8)
Acamprosate	*GATA4* (rs1327367)	Relapse	Kiefer et al., 2011 (10)
Disulfiram	*DBH* (rs161115)	Adverse events	Mutschler et al., 2012 (11)

*NOTE: OPRM1 predictive value for NTX response has been disproven (Oslin 2015 JAMA)

(Batki & Pennington (2014) *Am J Psychiatry*)

Some Salient Questions about AUD Pharmacotherapy

- What is the best measure of outcome?
  - Abstinence? Use reduction?
  - Quality of life?
  - Cognitive outcomes?
- Predictors?
- Best dose? (e.g. topiramate, oral NTX)
- Combinations of medications?
- Best route of administration, for whom?
- How long should treatment be continued?
- How to increase utilization?

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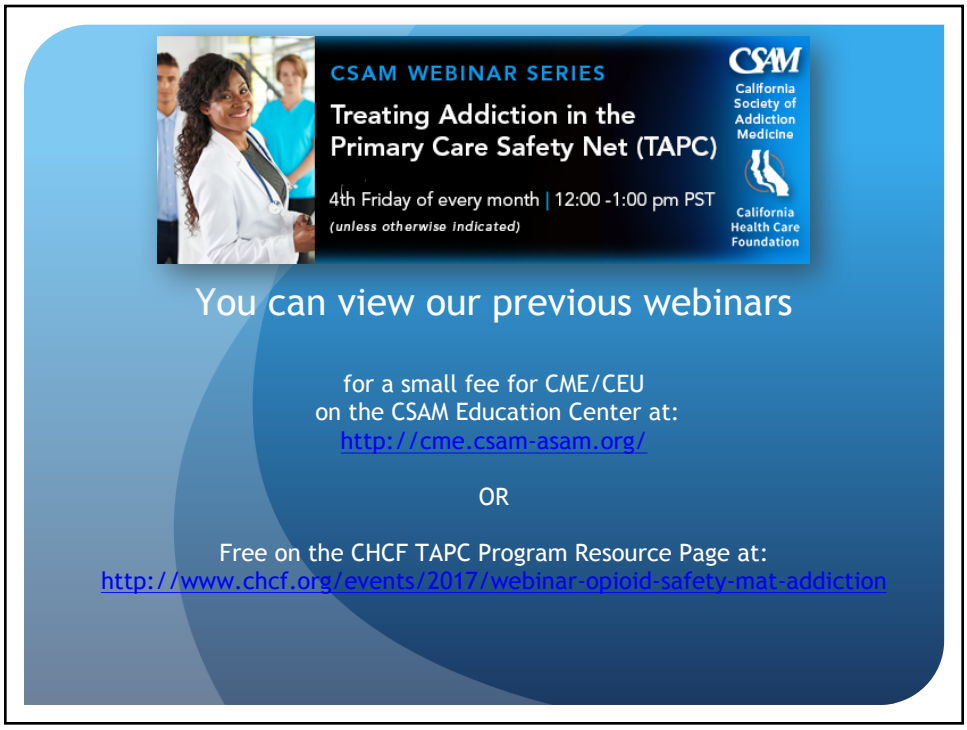
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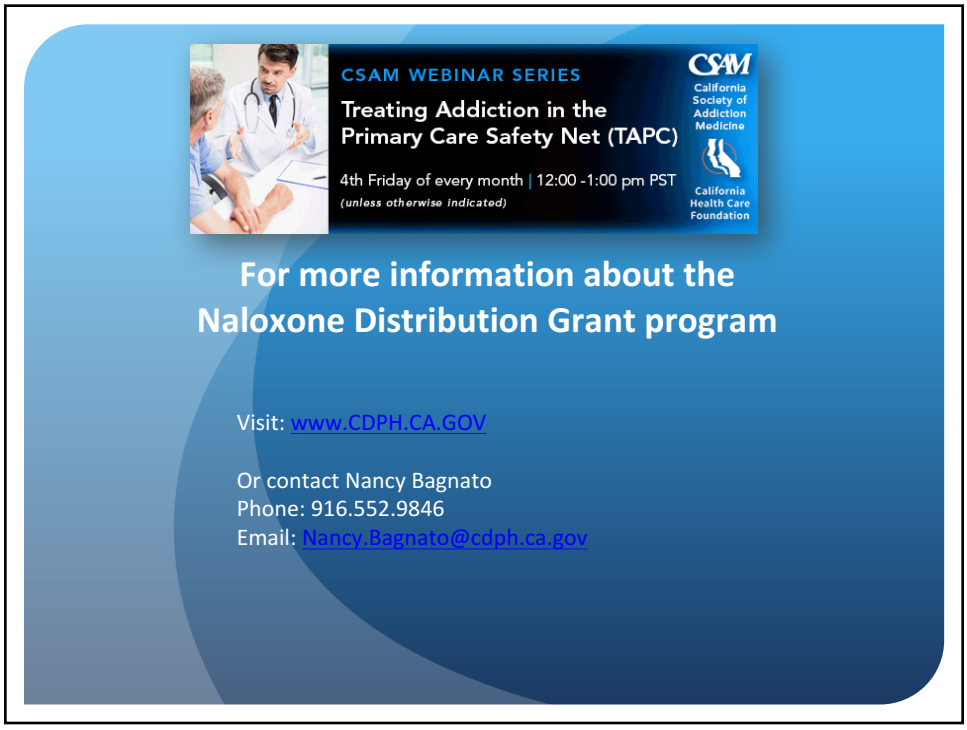
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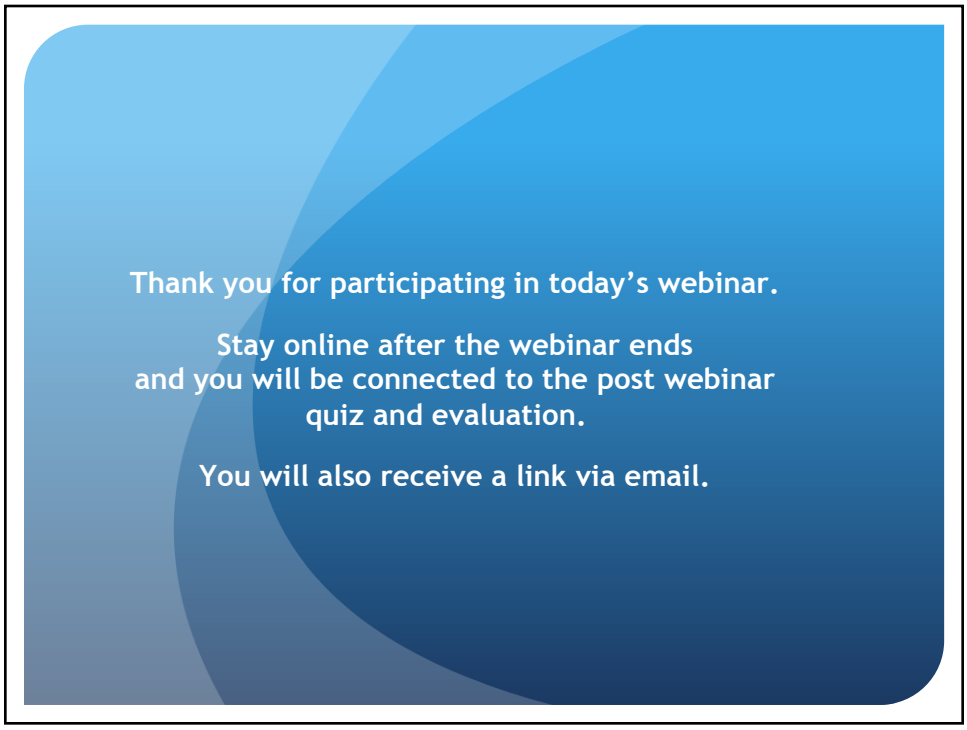
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