Injectable Extended-Release Naltrexone Disclosures & CME Credit

Neither the case presenter not the didactic presenter have conflicts of interest

Off label use of medications may be discussed

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InaccordancewiththeACCMEEssentials&Standards,anyoneinvolvedinplanningorpresentingthiseducationalactivitywillberequiredtodiscloseanyrelevantfinancialrelationshipswithcommercialinterestsinthehealthcareindustry.Thisinformationislistedbelow.Speakerswhoincorporateinformationaboutoff-labelorinvestigationaluseofdrugsordeviceswillbeaskedtodisclosethatinformationatthebeginningoftheirpresentation. Off-label use of naltrexone will be discussed and noted during the presentationNeedle

Medicine

Hospital

Brain in head

Brain in head

Naltrexone IndicationsCompetitive antagonist at the mu opioid receptor and to a lesser extent at the delta and kappa opioid receptors.

High affinity for receptor prevents the binding of opioid agonists and displace agonists if they are presentVolpicelli et al. Alc Health Res World. 1994;18:273

Naltrexone DosingOral Naltrexone for OUDNot Recommended

Cochrane review of 13 studies (1158 participants) compared naltrexone to placebo or no pharmacological treatment

no statistically significant difference in treatment retention or preventing return to opioid use

Poor adherence is a significant challenge

Oral use limited to:

Highly motivated, e.g. legally mandated to treatment

Aware of negative consequences of nonadherence

Observed dosing

Want to be on antagonist but unwilling or unable to take IMMinozzi et al. Cochrane Database

Syst Rev.2011 Feb 16;(2):CD001333

Duration

No recommended length of treatment with naltrexone.

Treatment less than 90 days is of limited effectiveness, and treatment lasting significantly longer is associated with more positive long-term outcomes.

Duration depends on patient response, clinical judgment & the patient's individual circumstances.

Can be stopped abruptly without withdrawal symptoms.

Contraindications

1. Hypersensitivity reactions to naltrexone or previous hypersensitivity reactions to polylactide-co-glycolide carboxymethylcellulose, or any other constituent of the diluent

2. Active hepatitis (LFTs are > 3x normal) or liver failure

3. Patients currently physically dependent on opioids, including partial agonists

4. Patients receiving opioid analgesics

5. Patients in acute opioid withdrawal

6. Failed naloxone challenge or UDS + for opioids

Administer IM with caution to patients with thrombocytopenia or a coagulation disorder

Cautions

1. Loss of tolerance.

2. Hepatic injury is a concern if very high doses are used, for example, 200–300 mg per day.

3. Transient, asymptomatic ↑ transaminases were also observed in the clinical trials & postmarketing period.

4. Patients with co-occurring psychiatric disorders should be monitored for adverse events. Suicidal thoughts, attempted suicide, and depression have been reported

5. Glyburide may increase serum concentration of naltrexone. Monitor for increased toxicity effects of naltrexone (e.g. liver LFTs). Metabolism

First pass metabolism in liver to 6β-naltrexol, a less potent μ antagonist with a longer duration of action

Elimination half-life:

Oral naltrexone 4 hours

6 β-naltrexol 14 hours

XR-NTX and 6β-naltrexol t ½ 5-10 days depending on erosion of the polymer

followed primarily by renal excretionRussian Multisite Double-Blind, Placebo-Controlled Randomized Trial XR-NTXChart

Description automatically generated

% of cumulative opioid free weeks

p=.0002

Mean change from baseline craving

p=.005

Krupitsky et al. Lancet. 2011;377:1506-13.

Outpatient Noninferiority Trial

12 week multisite open-label RCT in Norway

Following detoxification on detox unit randomized to:

Daily buprenorphine-naloxone 4-24mg (n=79)

Or XR-NTX 380mg IM every 4 weeks (n=80) Retention was non-inferior in ER-NTX vs. bup/nlx (p=.04)

ER-NTX ~70 days vs. bup/nlx ~ 64 days (p=.33)

Total opioid-negative UDSs noninferior

With superiority in lower use of heroin and other opioids (p=.001)

Tanum et al. JAMA Psychiatry. 2017; 4(12):1197-1205.

Comparison SL Buprenorphine-Naloxone vs Extended-Release Naltrexone (X:BOT)

Multisite, randomized, open label, controlled 6-month trial

Sublingual buprenorphine-naloxone, 8-24mg (N = 287)

Extended-release injection naltrexone (N = 283) Participants

OUD, Admitted to inpatient/residential treatmentRandomized as soon as possible after admission

For injection opioid detoxification had to be completed, urine negative for opioids, and pass naloxone challenge: “induction hurdle” Lee et al. Lancet 2018;391:309-318X-BOT: Relapse-free Survival & Treatment Effect over Time

Lee et al. Lancet 2018;391:309-318

XR-NTX had substantial induction hurdle: XR-NTX 72% vs. BUP-NTX 94%

Among those successfully inducted relapse rates were similar (p=.44)

Intent to Treat Population

Per ProtocolLee et al. Lancet 2018;391:309-318

X-BOT Opioid Craving

p=.001

p=0.2

Initiation to Avoid Precipitated Withdrawal

No or low opioid tolerance (post residential treatment or incarceration) could potentially start immediately pending negative UDS and COWS

Short-acting opioids: off about 6 days before starting naltrexone

Long-acting opioids: such as methadone and buprenorphine off opioids for typically 7–10 days or in some cases14 days

Naloxone or Naltrexone Challenge Test with recent useIM Administration

Needle

Needle

Adverse Reactions

≥ 5%& 2x more frequent than placebo

Nausea or vomiting

Injection site reactions (induration, nodules, swelling, pruritis) To minimize in obese patients use the provided longer needle and avoid SC admin

Decreased appetite or anorexia

Muscle cramps

Sedation

Dizziness or syncope ≥ 2% & 2x more frequent than placebo: abnormal LFTs, injection site pain, nasopharyngitis, injection site pain, & toothache

Postmarketing: additional injection site rxns included induration, cellulitis, hematoma abscess & necrosis. Some cases requiring surgical debridement

Rare: eosinophilic pneumonia, hypersensitivity rxn

Apart from opioids, it does not typically interact with other meds

Hepatoxicity

Historically commonly recommended to monitor patient's liver function (i.e., AST, ALT, GGT and bilirubin) at baseline and periodically

Hepatoxicity typically seen at oral doses closer to 300mg

Has not been problematic with daily oral naltrexone 50 mg or with the extended-release formulation and has been safely used in patients with liver disease, hepatitis C and HIV.

Current recommendation: not necessary to obtain baseline LFTs or routinely monitor LFTs. (SAMSHA 2016)

https://30qkon2g8eif8wrj03zeh041-wpengine.netdna-ssl.com/wp-content/uploads/2014/10/PCSS-MAT-NTX-Liver-Safety-Guideline1.pdf

Mitchell et al, 2012; J Stud Alcohol Drugs, 73(6), 991-997. Tertault et al. Alc Clin Exp Res. 2012;35:318-32. AEs: Depression & Suicidal Events (SI, SA, Completed Suicide)

Alcohol Dependence

Suicidal events 1% in Vivitrol group vs. 0% in placebo group

In 24-week RCT trial (n=624) depressed mood reported in 10% of XR-NTX compared to 5% in placebo group Garbutt et al. 2005

Opioid Dependence

Open-label US safety study 5% in Vivitrol (n=101) vs. 10% in oral naltrexone group (n=22)

In 24-week Russian RCT (n=250) no depressive or suicidal AEs in either groupKrupitsky et al. 2011

Pregnancy and Breastfeeding

Naltrexone and the 6-beta-naltrexol metabolite cross the placenta. Insufficient research on the safety and efficacy of naltrexone during pregnancy.

If a woman becomes pregnant while she is receiving naltrexone, it may be appropriate to discontinue if the patient and clinician agree that the risk of relapse is low.

If the patient chooses to discontinue naltrexone and is at risk for relapse, treatment with methadone or buprenorphine should be considered.

Insufficient research exists on the risks (if any) of naltrexone for breastfeeding infants. Limited data indicates that naltrexone is minimally excreted into breastmilk

Stroller

Surgery

Oral naltrexone should be discontinued 72 hours before surgery.

XR-NTX should be discontinued 30 days before an anticipated surgery with use of oral naltrexone until 72 hours prior to surgery. Transition from Naltrexone to Buprenorphine or Methadone

Patients will not have physical dependence on opioids and thus the initial doses of methadone or buprenorphine should be low.

Should not be transitioned until a significant amount of the naltrexone is no longer in their system, about 1 day for oral naltrexone or 28 days for XR-NTX.

Long-Acting Naltrexone Induction w Low Dose Naltrexone vs. Buprenorphine

Protocol Day

Naltrexone-assisted detox

Buprenorphine-assisted detox

1

Ancillary meds

2

Buprenorphine 4mg sl BID

3

washout

Buprenorphine 6mg

4

Naltrexone 1mg

Buprenorphine 4mg

5

Naltrexone 3mg

Buprenorphine 4mg

6

Naltrexone 12mg

Buprenorphine 2mg

7

Naltrexone 25mg

Buprenorphine 1mg

8

Extended-release naltrexone 380mg

15

Extended-release naltrexone 380mg

Ancillary meds offered

-clonidine 0.1mg QID

(+Q4HR PRN max 1.2mg)

-clonazepam 0.5mg QID

-prochlorperazine 10mg TID

-trazodone 100mg HS

-zolpidem 10mg HS

Sullivan et al. Am J Psychiatry 2017;174:459-467.

Long-Acting Naltrexone Induction w Low Dose Naltrexone vs. Buprenorphine

Protocol Day

Naltrexone-assisted detox

Buprenorphine-assisted detox

Completed

Induction

n=55 (56.1%)

n=17 (32.7%)

Completed trial (wk. 5)

n=51 (52%)

n=15 (28.8%)

2ndinjection

n=49 (50%)

n=14 (26.9%)

Sullivan et al. Am J Psychiatry 2017;174:459-467. Dermatologists' Solution for Low Dose Naltrexone

Crush naltrexone 50mg tabs and mix in water or orange juice

Refrigerated maintains stability for 90 days

Can taste bitter and gritty

For example, 2 tabs of naltrexone 50mg (100mg) crushed and dissolved in 100mg of orange juice = 1mg/ml solution

Bronfenbrener, R. (2019). Inexpensive compounding of low dose naltrexone (LDN) with orange juice.

J Am Acad Dermatol. https://doi.org/10.1016/j.jaad.2019.03.067. Cost

Oral: ~ $25 for 30 tabs of naltrexone 50mg

Vivitrol: ~ $1,400 excluding cost of visit

Covered by SOR funds

Alkermes patient assistance (up to $500 co-pay or deductible)

https://www.vivitrol.com/co-pay-savings-program

Pharmaceutical grade refrigerator to store

Can store at room temp (not above 77 °F) up to 7 days

Ability to give injections

Biomedical Waste1.

Have you been abstaining from other opiates & illegal drugs such as cocaine and speed?

2.Do you think you are able to cope with difficult situations without using drugs?

3.Are you employed or in school?

4.Are you staying away from contact with users & illegal activities?

5.Have you gotten rid of your drug paraphernalia?

6.Are you living in a neighborhood that doesn't have a lot of drug use & are you comfortable there?

7.Are you living in stable family neighborhood?

8.Do you have straight (non-user friends) that you spend time with? CSAT 1994

9.Do you have friends or family that would be helpful during a taper?

10.Have you been participating in counseling that has been helpful?

11.Does your counselor think you are ready to taper?

12.Do you think you would ask for help when you are feeling bad during a taper?

13.Have you been stabilized on buprenorphine?

14.Have you been on buprenorphine for a long time?

15.Are you in good mental and physical health?

16.Do you want to get off buprenorphine? Clinical Guide of ER-NTX in Treatment of Opioid Use Disorder: A Brief Guide

https://store.samhsa.gov/product/Clinical-Use-of-Extended-Release-Injectable-Naltrexone-in-the-Treatment-of-Opioid-Use-Disorder-A-Brief-Guide/SMA14-4892R

XR-Naltrexone: A Step-by-Step Guide

http://pcssnow.org/wp-content/uploads/2017/02/Naltrexone_Step-by-Step_Virtual_Brochure-1.pdf

Vivitrol REMS and Patient Medication Guide

https://www.vivitrol.com/content/pdfs/medication-guide.pdf

https://www.vivitrolrems.com/

Printable Wallet Card

https://www.vivitrol.com/content/pdfs/emergency-pain-management-card.pdf

pcssnow.org

Questions and Comments?

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Panel: TeleMAT Troubling Shooting During Covid-19

Panel Discussion

New Module

High Quality Medicated Assisted Treatment (MAT)

November 2020 –February 2021

11/6/20

What is High Quality MAT

Dr. Kelly Barth

11/20/20

Screening and SBIRT

Sarah Gainey, MSW

12/4/20

Motivation Interviewing

Dr. Elizabeth Santa Ana

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MAT in Primary Care: Med Management from POATS

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