Medication Is Addiction Treatment, Too!
An Overview Of Medication-Assisted Treatment

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Disclosure Information

David R. Gastfriend M.D., DFASAM

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IBM Watson/Truven Health Analytics, Rand Corp.
Purpose of the Webinar

- U.S. opioid crisis – epidemic proportions
  Society demands that we use every tool in the toolkit – that is not the case, so the burden is on us to change.
- FDA: approved 3 meds in addiction treatment (MAT) as safe & effective for opioid use disorder (OUD): methadone, buprenorphine, extended-release naltrexone.
- Each has unique chemistry, brain effects, side effects, and impact on behavior.
- We will review the superiority of MAT + counseling vs. counseling alone, principles for medicine selection, integration with psychosocial treatment, & adverse effects, abuse risks & treatment completion.

Objectives:

As a result of this workshop, participants will be able to:

- Describe the brain receptor actions and time-course of 3 FDA-approved meds in addiction treatment (MAT).
- Comprehend the scientific data on the efficacy & effectiveness of combined MAT + psychosocial treatment.
- Explain to patients/supportive others the role of MAT – what to expect and not to expect from each.
Brain Reward: With us throughout evolution

Myrick et al. Psychiatry 2008;65(4):466-475

fMRI Cue Activation by Alcohol Images

Social Drinkers  Alcohol-Dependent Individuals

Extended-release injectable naltrexone (XR-NTX) attenuates BOLD signal activation to olfactory and visual cues in detoxified alcohol-dependent volunteers

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2Harvard Medical School, Belmont, MA  3Alkermes Inc, Waltham, MA

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### Results: fMRI BOLD Signal Activation

XR-NTX Patients: 2 wks Post- vs. Pre-Treatment

XR-NTX appears to maintain abstinence
- Enhanced reactivity to conditioned cues may play a role in relapse
- XR-NTX decreased (blue pixels) cue reactivity to alcohol odors & photos
- Limitations: Modest sample size (N=31), non-clinical measures
Brain Structure:
Two Regions – Cortex & Limbic

Cortex
Role:
• Decision making
• Thinking
• Reasoning
• Learning

Limbic Region
Role:
• Basic Drives
• Experience of Reward, Euphoria

Interventions
– Psychosocial Therapies
– 12 Step Programs
– Monitoring

Interventions
– Agonist Medications
– Antagonist Medications

Brain Regions: Go & No-Go Roles

Both Reward/Motivation ("Go" signals) & Inhibitory Control ("No Go") disrupted in addiction – address BOTH in prevention & treatment

Healthy Opioid Receptor Activity

**Dopamine**
- Eating when hungry
- Drinking when thirsty
- Rewards survival behavior

**Endorphins**
- Pain relief
- Stress relief
- Emotional bonding


Opioid Agonists & Partial Agonists

**Agonists**
- Opioid analgesics
- Illicit opioid (e.g., heroin)
- Methadone
- Activates opioid receptors
- Excess dopamine release

**Partial Agonists**
- Buprenorphine
- Same as agonists, but ceiling effect

Opioid Antagonist

**Antagonist**
- Naltrexone
- Blocks opioid receptor
- Preferentially binds to the opioid receptors
- Displaces opioids
Brain Reward: Clinical Pharmacology

- Ventral Tegmental Area
- Nucleus Accumbens
- Dopamine
- Opioid Peptides
- Arcuate Nucleus
- GABA (Dopamine)

Naltrexone
Full and Partial Agonists vs. Antagonists

An agonist has an active site of similar shape to the endogenous ligand binding to the receptor and producing the same effect. An antagonist is close enough in shape to bind to the receptor but not close enough to produce an effect. It also takes up receptor space and so prevents the endogenous ligand from binding.

Opioid Effect

- **Full Agonist (Methadone)**
- **Partial Agonist (Buprenorphine)**
- **Antagonist (Naloxone)**

Neurobiology of Opioid Use Disorder

- **Opioids**: at substantia nigra & VTA interneurons, rapidly & briefly bind MOP-r, GABAergic inhibition of DA neurons
- **Dopaminergic Reward**: Initial positive reinforcement; later, regulatory changes via mRNA or protein/peptides
- **Recurrent withdrawal** negatively reinforces recurrent use, via regulatory changes that persist for weeks/months
- **Negative Reinforcement**: mediated via
  - Upregulation of the KOP-r/dynorphin system (may underlie aversion, dysphoria/anhedonia, and depression-like or anxiety-like states)
  - Stress-responsive brain areas via the hypothalamo-pituitary-adrenal (HPA) axis

(Kreek et al., J Clin Investigation 2012)
A Biopsychosocial Disorder Requires Treatment + Chemistry

Medications (All FDA-approved Agents)

Behavioral Therapies (Including Contingency Management)

Medical Detoxification Services

Recovery Support Services

Sanctions: measured, prompt, scientifically sound

"Ask your doctor if taking a pill to solve all your problems is right for you."
Goals of Anti-Opioid Pharmacotherapy

- **Withdrawal Management**: Not considered treatment; Detox without continued meds dominates; is *inadequate care*
- **Early recovery protection**: period of highest risk for OD
  - Death rates upon prison release = 12-100x that of general population
  - Harm reduction, e.g., from HIV and HEP C transmission
- **Anti-craving**: stabilize urges/impulses to permit counseling
- **Stress Response Normalization**: OUD disrupts ACTH/Cortisol
- **Extinction**: of both positive and negative cue response
- **Biological Stabilization**: Eating, diurnal cycle, sexual function, capacity for self-care / activities of daily living / treatment retention, general healthcare, relationship bonding
- **NOT Recovery**: Disease acceptance, coping skills, rehab

Drug-Drug Interactions

- Few with the currently MAT options,
  - But require prospective awareness/monitoring
  - Mostly relate to anti-HIV meds
- **Interactions with other opioids**
  - Agonists have risky interactions with sedative/hypnotics
- **Precipitated opioid withdrawal**
  - not a side effect, but is an adverse event
- **Encourage calls to report; help prescribers improve**
Adverse Events

- Side effects can occur with any medication
- AEs fall into basic categories:
  - Serious Adverse Events (SAEs) – rare, but need to anticipate them; may require ED
  - Routinely advise patients to expect common, mild to moderate side effects
- Of greatest concern early; mentoring helps
  - With experience, these become less frequent
- Phone mentors to report these episodes, so they can help improve success with detox and induction.

Methadone

- Full Mu-opioid agonist, slow onset & long duration (23 hrs)
- Extensive research shows benefit of treatment initiation
- Widely used in harm reduction: Anti-HIV & -HepC
- Start at 20-40 mg; titrating up until no craving or illicit use
- Average dose 80-100 mg daily
- Only in ~1,300 certified programs, per federal law
- Lipophilic, so fat tissue accumulation causes long withdrawal
- Must be used as a long-term treatment
- Cardiac risk:
  - Prolongs QTc
  - with risk of Torsades de Pointes
MOM IS GOING TO BE SO HAPPY WHEN SHE SEES THE GAS TANK FULL

**MMT: Impact on Treatment & Heroin Use**
During the 6 Mos. Post-release From Prison ± MMT (N=141)

<table>
<thead>
<tr>
<th></th>
<th>% of 180 days post-release in treatment</th>
<th>% of 180 days post-release used heroin</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>11%</td>
<td>85%</td>
</tr>
<tr>
<td>C+M</td>
<td>46%</td>
<td>64%</td>
</tr>
</tbody>
</table>


C = Counseling Only (N=70)
C+M = Counseling & Methadone Started in Prison (N=71)
Methadone: For Whom?

- Long history with chaotic lifestyle, psych illness, BZ use
- IV route of drug administration; high tolerance
- Needs close, daily supervision
- May have difficulty persisting with treatment
- High risk for diverting medication
- May benefit from take home contingency management
- Wants to continue some subjective sense of opioid dependence
- Has chronic pain problems & needs/expects opioids
- Pregnant or planning to become pregnant
- Is prepared for long-term or even lifelong dosing
Methadone & Buprenorphine Molecules

Methadone

Buprenorphine

Son

Dad

Generation Gap
**Buprenorphine**

- Partial agonist: ceiling effect, less OD
- Opioid activity: ~half of methadone’s
- Start patient in mild withdrawal (avoids provoking withdrawal)
- Slow onset, 36 hr-duration: reduces reinforcement
- Extensive research shows benefit of treatment initiation
- Prescribed daily, weekly or monthly in outpatient care
- Has greatly expanded access to care, but more is needed
- DEA Schedule C-III, requiring federal waiver, 100 patient limit
- Approved for opioid addiction (2002) as Subutex; now more commonly used as Suboxone (with naloxone in a 4:1 ratio)
- Generics (Zubsolv) & film preparations (Bunavail) approved
Treatment Retention in HIV+ Patients Receiving Buprenorphine/Naloxone (n=303)

Fiellin DA et al., JAIDS 2011; 56(Suppl 1) S33-S38.

Agonists: Treatment Retention

Agonists: Treatment Retention

Mean retention on BUP:

Yser, Addiction 2014: 66 days

Baser, AJMC, 2011: 69 days

Fishman, CPDD 2011: 67.2 days (adolescents/young adults)

Weiss, AGP 2011: 92% relapse within 60 days of taper

MMT vs. BUP: Retention (Flexible Dosing)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>buprenorphine</th>
<th>methadone</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Double-blind flexible dose studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson 2000</td>
<td>32</td>
<td>55</td>
<td>40</td>
<td>55</td>
<td>10.2%</td>
<td>0.08 [0.01, 1.06]</td>
</tr>
<tr>
<td>Mattick 2003</td>
<td>96</td>
<td>200</td>
<td>120</td>
<td>205</td>
<td>13.5%</td>
<td>0.02 [0.01, 0.09]</td>
</tr>
<tr>
<td>Politian 2001</td>
<td>15</td>
<td>27</td>
<td>28</td>
<td>31</td>
<td>7.9%</td>
<td>0.62 [0.43, 0.88]</td>
</tr>
<tr>
<td>Strain 1991a</td>
<td>47</td>
<td>84</td>
<td>45</td>
<td>80</td>
<td>10.4%</td>
<td>0.99 [0.76, 1.30]</td>
</tr>
<tr>
<td>Strain 1991b</td>
<td>13</td>
<td>24</td>
<td>15</td>
<td>27</td>
<td>5.1%</td>
<td>0.97 [0.59, 1.61]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>390</td>
<td>398</td>
<td>47.2%</td>
<td>0.83 [0.72, 0.95]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>203</td>
<td>248</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Chi² = 4.94, df = 4 (P = 0.29), I² = 19%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.63 (P = 0.009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **1.1.2 Open label flexible dose studies** |
| Fischer 1999 | 11 | 29 | 22 | 31 | 4.9% | 0.53 [0.32, 0.89] |
| Kintuensen 2005 | 9 | 25 | 21 | 25 | 4.4% | 0.43 [0.26, 0.74] |
| Lindosio 2004 | 38 | 81 | 42 | 77 | 9.2% | 0.96 [0.63, 1.47] |
| Mayur 2009 | 49 | 77 | 42 | 56 | 11.9% | 0.69 [0.48, 1.06] |
| Neri 2005 | 29 | 31 | 28 | 31 | 14.9% | 1.04 [0.89, 1.20] |
| Szky 2000bs | 28 | 64 | 34 | 76 | 7.5% | 0.98 [0.67, 1.42] |
| Subtotal (95% CI) | 380 | 296 | 62.9% | 0.80 [0.63, 1.02] |
| Total events | 164 | 189 |
| Heterogeneity: Tau² = 0.06, Chi² = 18.72, df = 5 (P = 0.002), I² = 73% |
| Test for overall effect: Z = 1.81 (P = 0.07) |

Total (95% CI) | 697 | 694 | 100.0% | 0.83 [0.73, 0.95] |
| Total events | 367 | 437 |

(Mattick et al., Cochrane 2014)
**MMT vs. BUP: Retention**

- 31 RCTs (N=5,430); evidence: mod to high
- Flexible dose MMT: better retention vs. BUP doses <16 mg
- BUP: when high dose MMT isn't tolerated
- BUP advantages: relative safety, alternate-day administration, convenience & access
- No need for more MMT vs. BUP RCTs

(Mattick et al., Cochrane 2014)

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**MMT vs. BUP: Cognitive Function**

**During Month 1 of Treatment:**

- Delayed reaction time & verbal memory deficits:
  Methadone > BUP > CTRLs (Rapeli P et al. ISAM 2006)

**After Maintenance is Established:**

- ≥ Reaction time: MMT 100 mg vs. CTRLs
  (Gordon, Psychopharm 1970)
- ▼ Working memory: MMT 70 mg (Mintzer & Stitzer, DAD 2002)
- ▼ Verbal memory: MMT 35 vs. 17.5 mg
  (Curran et al. Psychopharm 2001)
- ▼ Visual memory vs. CTRLs: MMT 66 mg & BUP 9 mg
  (Pirastu et al. DAD 2006)
- Driving reaction time delay: MMT > BUP
Buprenorphine: For Whom?

- Able to maintain a treatment plan without the daily supportive contacts/structure of a clinic
- Has structure in daily life (e.g., employed)
- Has a strong sober support system
- Has adequate stress management skills
- Pregnant women
- Patient with cardiac concerns (no QT prolongation)
- Wants less of a subjective sense of opioid dependence than with methadone
Extended-release naltrexone modulates brain response to drug cues in abstinent heroin-dependent patients

Daniel D. Langleben1,2, Kosha Ruparel1, Igor Elman1,2, James W. Loughead1, Elliot L. Busch1, James Cornish1,2, Kevin G. Lynch1, Elie S. Nuwayser, Anna R. Childress1 & Charles P. O'Brien1

Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; Veterans Administration Health Care System, Philadelphia, PA, USA; Department of Psychiatry, Harvard Medical School, Boston, MA, USA

ABSTRACT

Drug cues play an important role in relapse to drug use. Naltrexone is an opioid antagonist that is used to prevent relapse in opioid dependence. Central opioidergic pathways may be implicated in the heightened drug cue-reactivity, but the effects of the opioid receptors' blockade on the brain responses to drug cues in opioid dependence are unknown.
Results suggest...

- **limbic cue responses**
- **capacity for conscious self-regulation**

N=17 abstinent IV heroin users

pre- vs. post- 10–14 days after XR-NTX
Extended-Release Naltrexone

- Month-long mu-opioid competitive antagonism per IM injection
- Why?: Oral NTX meta-analysis: 13 RCTs (N=1158) NTX-PO did not reliably retain or abstinence rates. In Canada, NTX-PO associated deaths 3-7x > methadone (Minozzi et al., Cochrane 2011; Gibson AE, Degenhardt LJ, Drug Alc Rev 2007)
- XR-NTX: must be opioid-free 7-10 days (or rapidly detoxed)
- Detox causes loss of tolerance, patient must be cautioned
- Buttock muscle injection: site reactions; nausea, “NTX flu"
- Hepatic safety: even in chronic Hep C+ & HIV+; no black box
- No withdrawal upon treatment completion; self-tapering
- Not a controlled substance; no street value
- Treatment of choice for opioid + alcohol dependence

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**XR-NTX RCT: Abstinence, Retention, Craving**

<table>
<thead>
<tr>
<th></th>
<th>XR-NTX (n=151)</th>
<th>Placebo (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.4 (4.8)</td>
<td>29.7 (3.8)</td>
</tr>
<tr>
<td>Male</td>
<td>113 (99%)</td>
<td>103 (89%)</td>
</tr>
<tr>
<td>White</td>
<td>124 (99%)</td>
<td>124 (100%)</td>
</tr>
<tr>
<td>Duration of opioid dependence (years)</td>
<td>9.5 (4.5)</td>
<td>10.0 (3.9)</td>
</tr>
<tr>
<td>Days of pre-study medication detoxification</td>
<td>18 (10)</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Opioid tapering</td>
<td>18 (12)</td>
<td>22 (14)</td>
</tr>
<tr>
<td>HIV serology positive</td>
<td>51 (41%)</td>
<td>52 (42%)</td>
</tr>
<tr>
<td>Hepatitis C positive</td>
<td>111 (89%)</td>
<td>117 (84%)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (%). XR-NTX-extended-release naltrexone.

Table 1: Demographics and baseline clinical characteristics

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**XR-NTX: For Whom?**

- Motivated to undergo detox & be opioid-free
- Preparing to leave rehab or jail/prison opioid-free
- Monitored by judges, professional boards, employers, schools or sports teams that may not allow agonist treatment
- Structure & social supports in place (however, chronicity & severity can be either mild or severe)
- Rejects agonist treatment or has failed agonist treatment
- Succeeded with agonist treatment & wants to conclude it
- Wants shorter-term medication that can be easily concluded
- Late adolescent/emerging adult with shorter duration addiction
- Has both opioid and alcohol dependence

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**Percent of patients with Good Clinical Response**  
(≥ 90% urine-confirmed abstinent weeks)

<table>
<thead>
<tr>
<th>Baseline Predictor Variable</th>
<th>Percent of Patients with Good Clinical Response (&gt; 90% Urine-Confirmed Abstinent Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower Severity XR-NTX</td>
</tr>
<tr>
<td>Clinical Global Impression Severity (CGI-S)</td>
<td>58.6% (17/29)</td>
</tr>
<tr>
<td>SF-36 Mental Component</td>
<td>48.4% (31/64)</td>
</tr>
<tr>
<td>EQ-5D Health</td>
<td>58.0% (29/50)</td>
</tr>
<tr>
<td>Craving at Baseline</td>
<td>42.7% (29/68)</td>
</tr>
<tr>
<td>HIV Sero-status</td>
<td>HIV Negative</td>
</tr>
<tr>
<td></td>
<td>48.7% (36/74)</td>
</tr>
</tbody>
</table>

Descriptive analysis of baseline predictor-by-treatment interactions, significant at $p < 0.15$ – $0.05$. Baseline predictor variables that are continuous or count variables are dichotomized at the median split into lower and higher groups.

* None of the putative predictor variables yielded significant ($p<.05$) interactions with treatment.
6-Month Retention on XR-NTX: 3 Studies

Retention in Youth, Ages 15-24
Naturalistic treatment data, Baltimore MD (N=92)

(Fishman et al., SAMHSA-NIDA, 2016)
Healthcare Costs with MAT

- MMT, direct = $1/day  
- MMT, overall = $10-20/day  
- BUP = $4-$30/day  
- XR-NTX = $20-40/day

6-mo retrospective insurance cost study: all meds + inpt + outpt services  
(N=10,413) casemix controlled with with instrumental variable analysis

(P-value vs. XR-NTX: $P<0.001$

(Baser O, et al. AJMC 17: S235-S246, 2011)
KNOXVILLE, Tenn. (WATE) — Sixty-seven percent of fatal overdose victims with incarceration history within the last five years died within 18 months of their release from custody, according to a report by the Knox County District Attorney's Office.

**Multi-site Open RCT in CJ: Relapse**

![Graph showing the probability of relapse-free survival for extended-release naltrexone and usual treatment.](image)

(N=308)
Mortality Upon OUD Re-entry from Prison

- MMT & BUP ↓ OD & death rates, BUT...rates are increasing
  XR-NTX has OD/death risk – due to loss of tolerance
- Re-entry in OUD: death rates ↑ 12-100X; MMT & BUP ↓ this

3 XR-NTX RCTs in CJ:
- Coviello et al., Subst Abuse 2012 (N=61/2 mos.): 0 OD deaths
- Lee et al., NEJM 2016 (N=308/18 mos.): XR-NTX=0 ODs vs. TAU=7
- Springer et al., pers. comm. (preliminary N=94/12 mos.): 0 ODs/deaths; decreased HIV Viral Load

- Naloxone nasal spray or auto-injector: immediately reverses OD
  Should be supplied to ALL opioid users, families & 1st responders
  But – it is vital to then engage the patient in F/U & counseling
### XR-NTX Reports in Opioid Dependence

- Alkermes Sponsored/Funded Trials: 7
- Alkermes Provided Study Drug for Trials: 3
- Studies Conducted Independent of Alkermes: 5
- **Total Studies:** 15

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients Treated with XR-NTX</td>
<td>1,683</td>
</tr>
<tr>
<td>Est'd Total XR-NTX Patient x Months</td>
<td>5,719</td>
</tr>
</tbody>
</table>

- Reported Overdoses on XR-NTX: 4
- Reported Deaths from OD on XR-NTX: 0

### Med Discontinuation & Follow-Up

- Opioid substitution: necessarily long-term due to opioid withdrawal causing frequent relapse on discontinuation
- Vivitrol has no withdrawal symptoms; therefore, only needed as long as it takes to stabilize craving, establish acceptance of the disease, & engage in recovery
- Clinicians should work together with patients to determine how long MAT should be administered based on patient’s engagement in treatment, recovery efforts and functional progress.
- The model for assessment is the ASAM Criteria. The MAT Completion Protocol has been developed by Dr. Gastfriend on behalf of FADAA and DCF.
Post Medication Outcome Tracking

- OUD: chronic, relapsing
- Teams must track patients after MAT discontinuation
- Determine if patient may need to restart
- Preferably before physiological dependence reinstates
- Before other morbidity occurs
- During patient’s window of opportunity to re-engage.
- Physicians should get periodic follow-ups on post-MAT outcomes and advise re-MAT patient’s need to return for re-assessment and re-initiation of MAT.

Conclusions: Opioid Dependence

- OUD: a chronic disease needing long-term rehab with both meds AND counseling.
- Goals of treatment/rehabilitation: saving lives, stabilizing behavior & establishing social function
- Agonists & antagonists are superior to counseling alone
- All FDA-approved agents are appropriate 1st-line approaches
- Therefore, programs should provide ALL options, so that patients can be informed of and offered ALL options
- Low initial costs can become high costs longer-term
- High initial costs can result in lower costs longer-term
- Therefore, cost should NOT be a consideration
- Patient choice may be the BEST basis for drug selection.
- If one agent is unsuccessful, other options should be tried.
Opportunities: Agents & Formulations

- LAAM – full mu agonist; no longer used clinically
- XR morphine sulphate; Heroin-assisted treatment
- Heroin vaccine
- Probuphine 6 mo. BUP implant; FDA approval awaited

6-mo BUP Implant: Retention

![Graph showing Buprenorphine and Placebo retention over weeks.](image)

Ling, W. et al. JAMA 2010

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Addicted to a Treatment for Addiction

The New York Times

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Get The Times from $10.00 a month.
They Don’t Love You, Yeah Yeah Yeah

Musical geniuses, or “crowned heads of anti-music”? Quotes from Beatles critics over the decades

**KARL SHAW**

A pick-a-fight over any critics who have recently deserted a popular music band. (Beetles) In a lively dissection of the 2nd Beatles album.

**GUY PERGAMON**

“**The Beatles are NOT merely awful, I would consider it SACRILEGIOUS to say anything LESS than THAT THEY ARE GODAWFUL. THEY ARE SO UNBELIEVABLY HORRIBLE, SO APPALLINGLY UNMUSICAL, SO IDIOCRATICALLY INFERIOR TO THE MAGIC OF THE ART, THAT THEY QUALIFY AS CROWNED HEADS OF ANTI-MUSIC.**”

William F. Buckley, author and commentator, 1969

“MUSICALLY; they are a disaster. (Guitarist) Slammed out a careless beat that does away with secondary rhythm, harmony and melody. Brother (punctuated by nutty drum lines of “yeah, yeah, yeah!”) are a catastrophe, a pretentious farce of Tarantella and romantic sentiments.”

Newsweek reviewer Feb. 24, 1964

“THE BEATLES are the most repulsive group of men I’ve ever seen.”

David Susskind, American TV host, 1965

MY TEACHER always talks about the Beatles and they have no musical skills. My friend Rodney is a better player than these clowns. I think they should retire these songs with 50 Cent or Snoop. Then they won’t get any time behind them.”

Amazon.com customer review, 2005

“Looking back over the years, it’s hard not to always have a good idea and why you shouldn’t let Raino sing... if not the worst, then certainly the most overrated album of all time.”


“The Beatles laid the groundwork for most of our problems we have with young people by their stilted, unappealing music while entertaining in this country during the early and middle 1960s.”

Eliot Pecklen as recorded by the FBI memo 1969 to Richard Nixon House and FBI headquarters

“Love Me Do... a song waiting to be recorded that sounds like a fing exercise for prime school recorders”

Michael Dascal, author of this article, 2009
### Myths & Ethical Conundrums

- “Gold standard” = health, NOT necessarily abstinence
- MAT – “Medication-Assisted Treatment”: *stigmatizing*
  perhaps should be “Medication in Addiction Treatment”?
- Lifelong “Endorphin Deficiency”: little or no evidence
- MMT & OBOT “long term treatment” is not the norm
- Reinforcement: Critical & inadequately studied
- When MVAs peaked, U.S. mandated airbags, raising car costs by $1,000; OD deaths now surpass MVAs – what can we spend?
- Would we license autos that omit seat belts or headlights?
  Do we accredit hospitals for bypass surgery without cardiology?
- If other medical/surgical specialties must report 5-year outcomes, shouldn’t addiction treatment services?
- Is it ethical to mandate treatment + pharmacotherapy in CJ? Is it ethical NOT to?

### Specific Binding

- **[^18F]cyclofoxy (m ligand):**
  - 30-35% receptor occupancy for methadone >80 mg/day
  - Kling et al., JPET 2000

- **[^11C]carfentanil (m ligand):**
  - Bup 2mg: 27-47% occupancy
  - Bup 16 mg: 85-92% occupancy
  - Bup 32 mg: 94-98% occupancy
  - Greenwald, MK et al., Neuropsychoph 2003
Research Needs: We still need to know…

1. What are the criteria / protocols for MAT selection?
2. Is counseling even needed?
3. What’s the proper dose of Buprenorphine?
4. Is the patient taking the Buprenorphine?
5. How should we manage patient incentives & sanctions?
6. How do we manage pain?
7. What are the best protocols for antagonist induction?
8. What are the criteria & protocols for Rx conclusion / conversion?

Case Description Mishaps to Avoid…

- (Actual doctors’ writings from hospital charts)
- She has no rigors or shaking chills, but her husband states she was very hot in bed last night.
- She stated that she had been constipated for most of her life, until she got a divorce.
- Patient has chest pain if she lies on her left side for over a year.
- On the second day the knee was better, and on the third day it disappeared.
- Rectal examination revealed a normal size thyroid.
- The patient refused autopsy.
- Discharge status: Alive but without my permission.
Conclusions: Opioid Dependence

- Opioid Use Disorder: chronic disease, requires long-term rehabilitation & recovery supports with meds + counseling.
- The goals of treatment/rehabilitation: saving lives, stabilizing behavior and establishing social functioning.
- Agonists & antagonists are superior to counseling alone.
- All FDA-approved agents are appropriate 1st-line approaches.
- Therefore, programs should inform about & offer ALL options
- Low initial costs can become high costs longer-term, and high initial costs can result in lower costs longer-term, therefore, cost should NOT be a consideration in clinical care.
- BEST basis for drug selection: Patient choice
- If one agent is unsuccessful, try others!