
Substance Use Disorders

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DISCLOSURES	
Johnson & Johnson	Stock Holder

Substance Use Disorders

- **OVERVIEW OF ADDICTION TREATMENT**
 - THE IMPORTANCE OF SCREENING
 - THE ROLE OF MEDICATIONS
- **EVIDENCE-BASED PHARMACOTHERAPY**
 - NICOTINE ADDICTION
 - ALCOHOL ADDICTION
 - OPIATE ADDICTION
- **CONCLUSIONS**

Overview of Addiction Treatment

- **THE CHRONIC RELAPSING DISEASE MODEL**
 - LAPSES & RELAPSES
 - RECOVERY vs. CURE
- **PSYCHOTHERAPY**
 - RELAPSE PREVENTION THERAPY
 - COGNITIVE BEHAVIORAL THERAPY
 - MOTIVATIONAL ENHANCEMENT THERAPY
- **BUILDING A RECOVERY COMMUNITY**
 - TWELVE-STEP FACILITATION
- **ADDICTION PHARMACOTHERAPY**
 - DETOXIFICATION
 - MEDICATIONS FOR RELAPSE PREVENTION / CRAVING
- **TREAT CO-OCCURRING PSYCHIATRIC DISORDERS**

Substance Use Disorders

**Medications do not cure an addiction,
but
they may make recovery possible**

Substance Use Disorders

- **OVERVIEW OF ADDICTION TREATMENT**
 - **THE ROLE OF MEDICATIONS**
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Pharmacotherapy Strategies for Nicotine Dependence

- In 2007, an estimated 70.9 million Americans aged 12 or older were current (past month) users of a tobacco product.
- 70% of smokers want to quit
- Only 27% of doctors usually monitor their patients progress in quitting smoking
- 7% of smokers achieve long-term abstinence on their own
- With physician assistance, this increases to 30%

Pharmacotherapy Strategies for Nicotine Addiction

- **Nicotine Replacement Therapy (NRT)**
 - Nicotine gum or lozenge
 - Nicotine patch
 - Nicotine Inhaler
 - Nicotine nasal spray
- **Non- nicotinic therapies**
 - Bupropion SR
 - Varenicline (FDA May, 2006)

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– THE ROLE OF MEDICATIONS**
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ALCOHOLISM - EPIDEMIOLOGY

- **2nd MOST COMMON MENTAL DISORDER**
- **FIRST RANKING IN ADULT MALES (8%-10%)**
- **LIFETIME PREVALENCE IS 30% (DEP. OR ABUSE)
2001-02 NATIONAL EPIDEMIOLOGIC SURVEY ON
ALCOHOL & RELATED CONDITIONS (NESARC)**
- **HIGH INCIDENCE OF CO-MORBIDITY:**
 - **-37% OF ALCOHOL ABUSERS ALSO HAVE
MENTAL ILLNESS**
 - **53% OF DRUG ABUSERS ALSO HAVE MENTAL
ILLNESS**
- **25% TO 50% OF SUICIDES INVOLVE ALCOHOL**

SINGLE ALCOHOL SCREENING QUESTION (SASQ) – NIAAA GUIDE

“When was the last time you had more than 5 drinks in one day?” - (4 drinks for women)

Any positive response within the last year warrants assessment for problem drinking. Review all drinking during the last 28 days. Review DSM-IV criteria.

**(Canagasby & Vinson, Alcohol Alcohol, May-June 2005)
www.niaaa.nih.gov/guide Physician's Guide 7/19/05**

NEUROBIOLOGY OF ALCOHOL: CHRONIC ALCOHOL USE

- **UP-REGULATION OF NMDA RECEPTORS: EXCITATORY NEUROTRANSMISSION, PRIMARY CAUSE OF WITHDRAWAL SYMPTOMS**
- **DOWN-REGULATION OF INHIBITORY GABA RECEPTORS**
- **DOWN-REGULATION OF EXCITATORY DOPAMINE D-2 RECEPTORS**
- **INCREASED NOREPINEPHRINE ACTIVITY**

NEUROBIOLOGY OF ALCOHOL

EFFECTS OF ALCOHOL WITHDRAWAL:

- **CNS HYPERACTIVITY- NO OPPOSITION TO ALCOHOL INDUCED EXCITATORY STATE (NMDA HYPERACTIVITY)**
- **RELEASE OF CRF**
- **DELAYED RECOVERY OF D 2 RECEPTOR SENSITIVITY AFTER DETOX IS ASSOCIATED WITH HIGH RISK FOR RELAPSE**

ALCOHOL SUBTYPES (NESARC)

(adapted from Moss, Drug Alc Depend, June 2007)

<u>YOUNG ADULTS</u> 32%	<u>LATE ONSET</u> 38%	<u>EARLY ONSET</u> 30%
EPISODIC HEAVY DRINK.	MODERATE DRINKING	SEVERE CHRON. DRINKING
LITTLE PSYCHO-PATHOLOGY	MINIMAL PSYCHO-PATHOLOGY	SEVERE PSYCHO-PATHOLOGY
MINIMAL GENETIC RISK	MODERATE GENETIC RISK	SEVERE GENETIC RISK

Characteristics	Cluster 1 31.5%	Cluster 2 19.4%	Cluster 3 18.8%	Cluster 4 21.1%	Cluster 5 9.2%
Working Name	<i>“Young Adult Subtype”</i>	<i>“Functional Subtype”</i>	<i>“Intermediate Familial Subtype”</i>	<i>“Young Antisocial Subtype”</i>	<i>“Chronic Severe Subtype”</i>
Age Group	Young Adults	Middle Aged	Middle Aged	Young Adults	Middle Aged
Onset of AD from Drinking Initiation	2.8 yrs.	18.4 yrs.	15.0 yrs.	2.9 yrs	13.2yrs.
Multigenerational Familial Alcoholism			✓	✓	✓
Antisocial Personality Disorder				✓	✓
DSM-IV Alcohol Abuse Criteria				✓	✓
Mood Disorders			✓	✓	✓
Anxiety Disorders			✓	✓	✓
Regular Smoking			✓	✓	✓

TREATMENT OF MILD - MODERATE ALCOHOL WITHDRAWAL CIWA-Ar 8 to 20

LONG ACTING BENZODIAZEPINES:

- **CHLORDIAZEPOXIDE (Librium) 50 - 100 mg po q 6-8 hrs.**
- **DIAZEPAM (Valium) 10 - 20 mg po q 6-8 hrs.**

SHORT-ACTING BENZODIAZEPINES:

- **LORAZEPAM (Ativan) 2-4 mg po q 1- 4 hrs.**

TREATMENT OF SEVERE WITHDRAWAL **CIWA-Ar >20**

- **DIAZEPAM 10 mg IV**
 - REPEAT 5 mg IV q 5 min, until calm
- **LORAZEPAM 4 mg po q 1 hr, PRN or 2-4 mg IV, q 2-3 hrs or q 15 min till stable (impending DT's)**
 - MODERATE TO SEVERE LIVER DISEASE
 - ELDERLY OR CONFUSED PATIENTS
 - VERY ILL OR DEBILITATED PATIENTS
 - CAN BE GIVEN PO, IV OR IM

MEDICATIONS IN THE LONG-TERM **MANAGEMENT OF ALCOHOLISM**

- **DISULFIRAM ***
- **NALTREXONE (PO* & IM* formulations)**
- **ACAMPROSATE ***
- **TOPIRAMATE**
- **ONDANSETRON**
- **SSRIs**
- **QUETIAPINE / ARIPIPRAZOLE**

*** FDA APPROVED**

DISULFIRAM

- **DOSE: 500 mg po daily x 10 days; then 250 mg daily**
- **SIDE EFFECTS: drowsiness, headache, metallic taste, decreased libido/potency**
- **SUPPORTIVE COUNSELING NECESSARY**
- **Follow serial LIVER FUNCTION TESTS**
 - **monitor for ALCOHOL-INDUCED HEPATITIS**
- **Rx for Antabuse reaction: BENADRYL 50 mg IM or IV**

NALTREXONE

REDUCES ALCOHOL CRAVING AND RELASPE

- **DOSE: 50 mg to 100 mg daily WITH MEALS**
- **SIDE EFFECTS: NAUSEA & HEADACHE**
- **REVERSABLE HEPATOTOXICITY**
- **BEST WITH COMPLIANT PATIENTS**
- **REQUIRES COUNSELING (CBT) or REGULAR MD MONITORING VISITS (Project Combine, 2006)**
- **EFFICACY QUESTIONED IN WOMEN (O'Malley 2007)**

NALTREXONE OUTCOME
associated with variants of opioid
receptor gene OPRM 1

	Asp 40 Allel	Asn 40 Allel
NALTREXONE	87 % GOOD OUTCOME	55 % GOOD OUTCOME
PLACEBO	49 % GOOD OUTCOME	54 % GOOD OUTCOME

(Project Combine; R. Anton, ARCH GEN PSYCHIATRY, 2008)

NALTREXONE

- **LONG-ACTING INJECTABLE FORMULATION**
 - 380 mg IM EVERY 28 DAYS
- **SCREEN LFT's**
- **MORE STABLE PLASMA CONCENTRATION COMPARED TO THE ORAL FORMULATION**
- **SIDE EFFECTS: NAUSEA & HEADACHE**
- **BEST RESULTS IN PATIENTS SOBER ONE WEEK PRIOR TO STARTING MEDICATION**

ACAMPROSATE

- **ALTERS GABA & NMDA SYSTEMS**
- **NO TOLERANCE, WITHDRAWAL OR SEDATION**
- **REDUCES ALCOHOL CRAVING & RELAPSE**
- **MINIMAL SIDE EFFECTS (MILD DIARRHEA)**
- **EXCRETED THRU THE KIDNEYS**
- **NO DRUG-DRUG INTERACTIONS**
- **DOSE: 666 MG PO TID**

PROJECT COMBINE

1383 PATIENTS RANDOMIZED TO VARIOUS COMBINATIONS OF NALTREXONE, ACAMPROSATE, COMBINED BEHAVIORAL INTERVENTION (CBI) AND MEDICAL MANAGEMENT (MM)

- **ALL GROUPS IMPROVED**
- **NALTREXONE / MM BEST OUTCOME**
 - **ADDING CBI DID NOT IMPROVE RESULTS**
 - **ADDING ACAMPROSATE DID NOT IMPROVE RESULTS**
- **ONE YEAR OUTCOME: NO SIGNIFICANT DIFFERENCE AMONG GROUPS**

JAMA. 2006;295(2003-2017)

TOPIRAMATE

- **FACILITATES GABA**
- **INHIBITS GLUTAMATE**
- **REDUCED DRINKING AND CRAVING:**
 - **DBCP TRIAL** (Johnson, Lancet, 2003)
 - **150 SUBJECTS**
- **DOSE: 25 mg po daily, THEN UP TO 100 mg tid**
- **SIDE EFFECTS: FATIGUE & COGNITIVE DULLING**
- **REPLICATED IN 371 SUBJECTS, DBPC-RANDOMIZED TRIAL (Johnson, JAMA, 2007)**

ONDANSETRON

- **ANTI-NAUSEA DRUG APPROVED 1991**
- **SELECTIVE 5-HT₃ BLOCKER**
- **REDUCED DRINKING IN EARLY-ONSET ALCOHOLISM (TYPE II)**
- **DOSE: 4 microgm/kg po BID**
- **DBPC 11 WEEK TRIAL; 321 PATIENTS**
- **LESS EXPENSIVE GENERIC VERSION NOW AVAILABLE - 2008**

(BA JOHNSON, JAMA AUG 23, 2000)

SSRIs MAY REDUCE DRINKING IN SOME ALCOHOL SUBTYPES

- **CITALOPRAM:** Reduced drinking in non-depressed male alcoholics; no efficacy in non-depressed female alcoholics (Naranjo, 2000)
- **SERTRALINE:** Reduced drinking in Type A men (late onset); no efficacy in Type A women or Type B men or women (Pettinati, 2004)

QUETIAPINE

- **ATYPICALS TARGET BOTH DA & 5-HT SYSTEMS**
 - **REDUCED SUBSTANCE USE ON CLOZAPINE**
 - **12-WEEK DBPC TRIAL IN 61 SUBJECTS**
 - **11 OF 61 ACHIEVED TOTAL ABSTINENCE:**
 - 9 WERE ON QUETIAPINE
 - 2 WERE ON PLACEBO
 - **TYPE B – MARKED QUETIAPINE BENEFIT**
 - **TYPE A – NO DIFFERENCE FROM PLACEBO**
- Kampman & Pettinati, J Clin Psychopharmacology, 2007

ALCOHOLISM: **RANK OF CO-MORBID CONDITIONS**

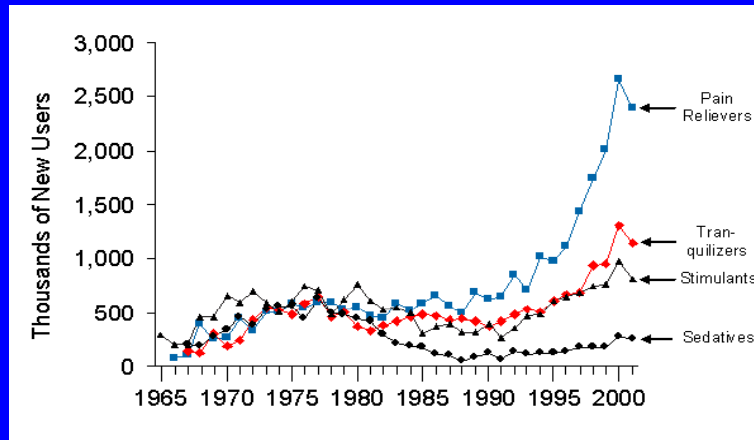
1. ABUSE OF A SECOND SUBSTANCE
2. ANTISOCIAL PERSONALITY DIS.
3. PHOBIAS (& OTHER ANXIETY DIS.)
4. MAJOR DEPRESSIVE DISORDER
5. DYSTHYMIC DISORDER

NOTE: CO-MORBIDITY IS THE NORM
FOR MOST ALCOHOLICS SEEN IN
ANY CLINICAL SETTING

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Annual Numbers of New Nonmedical Users of Psychotherapeutics: 1965–2001



From: 2002 National Survey on Drug Use and Health,
SAMHSA

Substance Use Disorders

Drug Abuse Screening

- Urine Toxicology
- NIDAMED www.drugabuse.gov/nidamed/

NEUROBIOLOGY OF OPIOID WITHDRAWAL

- **HYPERACTIVITY OF NOR-ADRENERGIC NEURONS IN LOCUS COERULEUS**
 - INCREASE BP, HR, RESPIRATIONS
 - INCREASE SWEATING, DIARRHEA
 - CLONIDINE & OPIATES REVERSE THESE EFFECTS
- **INCREASED GABA EFFECTS: REDUCED DOPAMINE IN NUCLEUS ACCUMBENS**
 - CAUSES DYSPHORIA, DEPRESSION, CRAVING
 - ONLY OPIATES REVERSE THESE EFFECTS

METHADONE DETOXIFICATION

- Treat AFTER documenting WITHDRAWAL
- DO NOT EXCEED INITIAL dose of 20 mg methadone (10 mg in younger addicts)
- May repeat in 2 hrs. if withdrawal increases. Inpatients rarely require over 40mg/24 hours
- Monitor QTc interval
- TITRATE DOSE to avoid intoxication or withdrawal
- DETOX TAPER: cut 10 mg/day down to 20 mg, then 5 mg/day down to zero

BUPRENORPHINE DETOXIFICATION

- DOCUMENT WITHDRAWAL BEFORE 1ST DOSE
- DAY 1: BUP/NALOXONE 4/1 mg SL, MAY REDOSE in 2 TO 4 HRS, UP TO 8/2 mg SL
- DAY 2: 8/2 to 12/3 mg SL
- DAY 3: 6/1.5 mg SL, final dose; may also taper
- 7 DAY PROTOCOL MAY BE MORE EFFECTIVE
- ADDICTS PREFER BUPRENORPHINE OVER METHADONE OR CLONIDINE -

Umbricht, 2003

CLONIDINE FOR OPIATE DETOX **SUPPRESSES FIRING OF LOCUS COERULEUS**

- FROM MAINTENANCE: REDUCE METHADONE TO 20 MG, THEN CLONIDINE 0.2 - 0.3 MG QID, THEN TAPER, 10 DAYS OR LESS
- FROM HEROIN: 5 mcg/kg/day x 5 DAYS, THEN TAPER
- SIDE EFFECTS: HYPOTENSION & SEDATION
- WILL NOT SUPPRESS ALL SUBJECTIVE SYMPTOMS
- LOFEXIDINE HAS FEWER SIDE EFFECTS

DETOXIFICATION OUTCOME DATA

percent patients drug-free at 13 weeks

NIDA CTN Network - Ling, 2005

MEDICATION	INPT DETOX	OUTPT DETOX
BUPRENORPINE / NALOXONE	77%	29%
CLONIDINE	22%	5%

OPIOID SUBSTITUTION THERAPY

METHADONE:

- **REGS REQUIRE 1 YEAR ADDICTION HISTORY**
- **60 TO 120 mg daily**
- **BEST FOR ADDICTS WITH LARGE HABITS AND LESS MOTIVATION**
- **MAY INDUCE PROLONGED QTc – MUST MONITOR**
- **IS METABOLIZED BY CYP3A4: MONITOR TROUGH LEVELS - AIM FOR 400 ng / ml**
- **ANALGESIA NEEDS: MAINTENANCE PATIENTS DO EXPERIENCE PAIN. WILL NEED ADDITIONAL OPIOIDS FOR PAIN**
- **HIGH DOSES MAY REDUCE TESTOSTERONE**

OPIOID SUBSTITUTION THERAPY

BUPRENORPHINE:

- PARTIAL OPIATE AGONIST
 - LOW OVERDOSE RISK
 - “CEILING EFFECT”
- SUBLINGUAL BUP / NALOXONE TABLET
- LEGAL FOR ADDICTS WITH LESS THAN 1 YEAR ADDICTION HISTORY
- OFFICE-BASED TREATMENT OPTION
- 300,000+ ADDICTS CURRENTLY IN TREATMENT
- PRESCRIBING REQUIRES TRAINING & CSAT / DEA WAIVER

OPIOID SUBSTITUTION THERAPY

BUPRENORPHINE:

- DSM-IV CRITERIA FOR ADDICTION
- CAN TREAT PATIENTS AGE 16 AND OLDER
- RAPID STABILIZATION IN 2-3 DAYS
- MAINTENANCE RANGE: 12-32 MG
- LONG HALF-LIFE: 24 TO 72 HR DOSING
- BEST OPTION FOR YOUNGER, MOTIVATED ADDICTS WITH SHORTER ADDICTION HISTORIES AND LESS SOCIOPATHY
- NOT RECOMMENDED IN SEVERE CHRONIC PAIN SYNDROMES

IMPROVING RESULTS IN OPIOID SUBSTITUTION THERAPY

- **USE ADEQUATE DOSES: MONITOR
METHADONE TROUGH LEVELS**
- **PROVIDE SKILLED PSYCHOTHERAPY AND
ANCILLARY SERVICES**
- **TREAT OTHER PSYCHIATRIC DISORDERS**
- **QUICKLY REWARD CLEAN URINES AND
IMPROVED BEHAVIOR**
- **LONG-TERM / INDEFINITE TREATMENT**

NARCOTIC ANTAGONIST THERAPY

- **NALTREXONE: 50 mg PO daily**
- **WORKS ONLY IN VERY MOTIVATED
& STABLE PATIENTS**
- **DEPOT NALTREXONE MAY PROVE
USEFUL OPTION**

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PATIENT MANAGEMENT TECHNIQUES

The Chronic Disease Model

- **SOBRIETY IS THE PRIMARY GOAL**
- **SUPPORTIVE CARE - BUILD DEFENSES**
- **LEARN TO WORK WITH A.A./N.A.**
- **CBT & RELAPSE PREVENTION**
- **ANTICIPATE LAPSES & RELAPSES**
- **ACTIVE THERAPEUTIC STANCE**
- **MEDICATIONS FOR RELAPSE / CRAVING**
- **TREAT CO-MORBID PSYCHIATRIC DISORDERS**