

THE TOP 20 SUBSTANCE ABUSE ARTICLES OF 2009: WHAT PHYSICIANS WERE READING OVER THE PAST YEAR

The amount of research concerning adult substance abuse is rapidly increasing, but lagging for adolescents. Still, it is important 1) to know what was reported scientifically last year that can guide your practice and 2) to know what your medical doctor friends are reading.

I have summarized the top 20 articles from MDLINX.COM, rather than just the top 10, because there are another 10 that are helpful.

I have included the abstract and the source of the original article.

At the beginning of most of these abstracts, I include my comments to point out the significance for your practice.

Note:

1. The Major "Take-Home Points" of each abstract are in CAPS BOLD
2. You can contact CESAR to obtain a copy of the full article
3. You can go to this link to view the top 50 articles:
http://www.mdlinx.com/psychlinx/index.cfm?selectedTab=4&subspec_id=79

Happy New Year,

Peter R. Cohen M.D., Medical Director, ADAA, January 4, 2010

1. [Cannabis and anxiety: a critical review of the evidence](#)

Fusar-Poli P et al. Human Psychopharmacology: Clinical and Experimental, 08/21/09

Comment: Cannabis and anxiety disorders feed on each other but it is still unclear if cannabis leads to chronic anxiety disorders. The person smokes pot at his or her risk, but should also be treated for anxiety, which can be very disabling.

Background: Anxiety reactions and panic attacks are the acute symptoms most frequently associated with cannabis use. Understanding the relationship between cannabis and anxiety may clarify the mechanism of action of cannabis and the pathophysiology of anxiety. Aims of the present study were to review the nature of the relationship between cannabis use and anxiety, as well as the possible clinical, diagnostic and causal implications.

Method: Systematic review of the Medline, PsycLIT and EMBASE literature.

Results: Frequent cannabis users consistently have a high prevalence of anxiety disorders and patients with anxiety disorders have relatively high rates of cannabis use.

HOWEVER, IT IS UNCLEAR IF CANNABIS USE INCREASES THE RISK OF

DEVELOPING LONG-LASTING ANXIETY DISORDERS. Many hypotheses have been proposed in an attempt to explain these relationships, including neurobiological, environmental and social influences.

Conclusions: THE PRECISE RELATIONSHIP BETWEEN CANNABIS USE AND ANXIETY HAS YET TO BE ESTABLISHED. Research is needed to fully clarify the mechanisms of such the association.

Copyright © 2009 John Wiley & Sons, Ltd.

2. [A Double-Blind Trial of Gabapentin Versus Lorazepam in the Treatment of Alcohol Withdrawal](#) (Neurontin versus Ativan)

Comment: This is the great battle between Neurontin and Ativan, between a substance that is not potentially addictive and one that is.

First, a comment about research methods. This four day withdrawal regimen involved patients not knowing which medication they were taking. The results are even more impressive when your research involves this many individuals. Usually you want to have at the least 15 in each group. The more the better. And even if the results are positive, some other researcher should try to repeat the study.

Gabapentin (Neurontin) should be seriously considered over Lorazepam (Ativan), for successfully treating EtOH withdrawal: 1. It was tolerated well by patients. 2. Withdrawal was successfully completed without danger or significant discomfort and with better withdrawal rating scores over time. 3. Neurontin had less craving, anxiety, and sedation associated with its use. 4. And here's the clincher: the chance of drinking in the next week after the four days of withdrawal were significantly less than there was with Ativan. This positive benefit cannot be explained by the half-life of Neurontin which is 5-7 hours versus Ativan's 14 hours (how long it takes for 1/2 of the substance to be no longer in the bloodstream where it can still have an effect on the brain).

And what about the price, since both can be prescribed as the generic? By my calculations, over four days: Gabapentin: \$8.25 Lorazepam: \$7.30

Both meds can be prescribed in the Maryland Medicaid system through the mental health carve-out.

Myrick H. et al. Alcoholism, 06/01/09.

Introduction: Some anticonvulsants ameliorate signs and symptoms of alcohol withdrawal, but have an unacceptable side effect burden. Among the advantages of using anticonvulsant agents in this capacity is their purported lack of interaction with alcohol that could increase psychomotor deficits, increase cognitive impairment, or increase intoxication. The aim of this study was to evaluate alcohol use and symptom

reduction of gabapentin when compared with lorazepam in the treatment of alcohol withdrawal in a double-blinded randomized clinical trial.

Methods: One hundred individuals seeking outpatient treatment of alcohol withdrawal with Clinical Institute Withdrawal Assessment for Alcohol–Revised (CIWA–Ar) ratings ≥ 10 were randomized to double-blind treatment with 2 doses of gabapentin (900 mg tapering to 600 mg or 1200 tapering to 800 mg) or lorazepam (6 mg tapering to 4 mg) for 4 days. Severity of alcohol withdrawal was measured by the CIWA–Ar on days 1 to 4 of treatment and on days 5, 7, and 12 post-treatment and alcohol use monitored by verbal report and breath alcohol levels.

Results: CIWA–Ar scores decreased over time in all groups; high-dose gabapentin was statistically superior but clinically similar to lorazepam ($p = 0.009$). During treatment, lorazepam-treated participants had higher probabilities of drinking on the first day of dose decrease (day 2) and the second day off medication (day 6) compared to gabapentin-treated participants ($p = 0.0002$). Post-treatment, gabapentin-treated participants had less probability of drinking during the follow-up post-treatment period ($p = 0.2$ for 900 mg and $p = 0.3$ for 1200 mg) compared to the lorazepam-treated participants ($p = 0.55$). The gabapentin groups also had less craving, anxiety, and sedation compared to lorazepam.

Conclusions: GABAPENTIN WAS WELL TOLERATED AND EFFECTIVELY DIMINISHED THE SYMPTOMS OF ALCOHOL WITHDRAWAL IN OUR POPULATION ESPECIALLY AT THE HIGHER TARGET DOSE (1200 MG) USED IN THIS STUDY. GABAPENTIN REDUCED THE PROBABILITY OF DRINKING DURING ALCOHOL WITHDRAWAL AND IN THE IMMEDIATE POSTWITHDRAWAL WEEK COMPARED TO LORAZEPAM.

3. [Ceftriaxone Restores Glutamate Homeostasis and Prevents Relapse to Cocaine Seeking](#)

Knackstedt LA et al. Biological Psychiatry, 09/08/09

Comment: The awards season is upon us once again, reinforcing the narcissism of the entertainment profession. If we had award shows, this might get the “WHAH!?!?” trophy for “The Most Off-Putting Title of 2009.” But it is important.

Cocaine addiction and relapse are very hard to treat. We need to do better finding ways to suppress the rampant cravings for cocaine. And our current efforts of rehab treatment and self-help are not winning accolades for hitting at least 50% success over the short-run.

Ceftriaxone (Rocephin) is an antibiotic used in the treating bacterial infections. In this study it was used experimentally to treat cocaine seeking. THIS PROMISING RESEARCH SHOWS THAT THIS ANTIBIOTIC CAN RESTORE THE ACTIVATING BRAIN TRANSMITTER GLUTAMATE, WHICH HAS BEEN DEPLETED BY COCAINE USE. As a result, it might be a helpful medication in preventing cocaine relapse. On the other hand, the chronic use of antibiotics can lead to superbacterial infections, which is what happens when bacteria resist the killing effects of antibiotics and continue to do damage or cause death.

Background : The cystine-glutamate exchanger is downregulated after chronic cocaine, resulting in reduced extracellular levels of nucleus accumbens glutamate. The importance of cocaine-induced loss of glutamate homeostasis is revealed by N-acetylcysteine restoring cystine-glutamate exchange and attenuating reinstatement to cocaine seeking. Another regulator of extracellular glutamate is the glial glutamate transporter GLT-1. We hypothesized that cocaine self-administration reduces GLT-1 and that GLT-1 upregulation inhibits cocaine seeking.

Methods: We measured [3H] glutamate uptake and protein expression of GLT-1 and xCT, the catalytic subunit of the cystine-glutamate exchanger, following cocaine self-administration and 3 weeks of extinction training. We also examined the affect of ceftriaxone (previously shown to increase GLT-1) and N-acetylcysteine treatment on the expression of GLT-1 and xCT. Ceftriaxone was also tested for the capacity to inhibit cue- and cocaine-induced relapse.

Results: Cocaine self-administration reduced glutamate uptake and the expression of both GLT-1 and xCT. Ceftriaxone restored GLT-1 and xCT levels and prevented cue- and cocaine-induced reinstatement of drug seeking. N-acetylcysteine also restored GLT-1 and xCT levels.

Conclusions: These results indicate that glutamate transport and cystine-glutamate exchange may be coregulated and provide further evidence that targeting glutamate homeostasis is a potential method for treating cocaine relapse.

4. [Cannabis use and age of diagnosis of schizophrenia](#)

Sugranyes G et al. European Psychiatry , 07/17/09

Comment: This study confirms that in vulnerable people, schizophrenia will appear at an earlier age if she or he has been using cannabis and at a higher frequency. The results from this study are significant because 60% with schizophrenia were using pot, and 40% on a daily basis. Consider that teens vulnerable to schizophrenia because of genetics, for example, are more likely to develop the disease earlier when using marijuana. From a prevention basis, it still makes sense to help young people delay the onset of the use of substances as long as possible, during those years when the brain is still developing and vulnerable to a number of mental disorders and substance use problems.

Background and objectives: Observational studies have reported earlier onset of psychosis in schizophrenic patients with a history of cannabis use. Earlier age of onset of schizophrenia has been associated with a poorer outcome. We aimed to examine whether cannabis use determined an earlier onset of schizophrenia in a sample of first episode patients, in an area with one of Europe's highest rates of cannabis use.

Methods: 116 subjects with first episode psychosis and subsequent diagnosis of schizophrenia (after a 12-month follow-up) were included Age at first antipsychotic treatment (A1T) was used as proxy for age of psychosis onset, and acted as dependent variable for the statistical analysis. Cannabis use was evaluated retrospectively, and divided into three groups according to peak frequency (never, sporadic/frequent, daily).

Results: 46 (39.7%) subjects had never used cannabis, 23 (19.9%) had done so sporadically/frequently, and 47 (40.5%) daily. A1T differed between the three groups (mean, in years and [SD]: 27.0 [4.94]; 25.7 [4.44] and 24.5 [4.36]; $p = 0.033$) and diminished as cannabis use increased (linear tendency; $p = 0.009$). Post-hoc analysis showed that cannabis use (irrespective of frequency) was significantly associated with decrease in A1T ($p = 0.033$), as shown by the first contrast [1 -1/2 -1/2]. Post-hoc contrast showed that cannabis users had a significantly lower age of onset of psychosis (mean decrease, in years: 1.93; CI (confidence interval) 95%: 0.17–3.70; $p = 0.033$).

Conclusions: CANNABIS USE WAS SIGNIFICANTLY ASSOCIATED WITH A DECREASE IN AGE OF ONSET OF SCHIZOPHRENIA. AGE OF ONSET OF THE DISEASE CORRELATED WITH FREQUENCY OF CANNABIS USE.

5. Randomized, Double-Blind, Placebo-Controlled Trial of Vigabatrin for the Treatment of Cocaine Dependence in Mexican Parolees

Brodie JD et al. American Journal of Psychiatry, 08/07/09

Comment: This study shows that some cocaine dependent persons (28%) might become abstinent in the short run with this non-addicting anti-seizure medication that raises GABA levels. GABA is the brain transmitter that has a calming effect. Benzodiazepines, which are potentially addictive, will raise GABA levels. That's why they calm the person, but at a price. Note that Vigabatrin may help promote abstinence from cocaine and from alcohol, but it does not seem to reduce drug craving.

OBJECTIVE: Cocaine dependence is associated with severe medical, psychiatric, and social morbidity, but no pharmacotherapy is approved for its treatment in the United States. The atypical antiepileptic vigabatrin (7-vinyl gamma-aminobutyric acid [GABA]) has shown promise in animal studies and open-label trials. The purpose of the present study was to assess the efficacy of vigabatrin for short-term cocaine abstinence in cocaine-dependent individuals.

METHOD: Participants were treatment seeking parolees who were actively using cocaine and had a history of cocaine dependence. Subjects were randomly assigned to a fixed titration of vigabatrin (N=50) or placebo (N=53) in a 9-week double-blind trial and 4-week follow-up assessment. Cocaine use was determined by directly observed urine toxicology testing twice weekly. The primary endpoint was full abstinence for the last 3 weeks of the trial.

RESULTS: Full end-of-trial abstinence was achieved in 14 vigabatrin-treated subjects (28.0%) versus four subjects in the placebo arm (7.5%). Twelve subjects in the vigabatrin group and two subjects in the placebo group maintained abstinence through the follow-up period. The retention rate was 62.0% in the vigabatrin arm versus 41.5% in the placebo arm. Among subjects who reported prestudy alcohol use, vigabatrin, relative to placebo, was associated with superior self-reported full end-of-trial abstinence from alcohol (43.5% versus 6.3%). There were no differences between the two groups in drug craving, depressed mood, anxiety, or Clinical Global Impression scores, and no group differences in adverse effects emerged.

CONCLUSIONS: THIS FIRST RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL SUPPORTS THE SAFETY AND EFFICACY OF SHORT-TERM VIGABATRIN TREATMENT OF COCAINE DEPENDENCE.

6. [A Randomized, Double-Blind, Placebo-Controlled Pilot Study of Naltrexone in Outpatients With Bipolar Disorder and Alcohol Dependence](#)

Brown ES et al. Alcoholism, 08/13/09

COMMENT: Naltrexone (brand name: Revia or IM Vivitrol) blocks the effects of opiates, and it can help reduce alcohol craving and drinking days in persons who also have bipolar disorder. This can be especially helpful for those who chronically relapse on alcohol despite rehabilitation or self-help groups. I call this cutting the person a break so that they can recover. Remember that we need to be on guard when we see someone with a combination of bipolar disorder and alcoholism. This duo can be very lethal. Finally, persons with bipolar disorder also have the highest frequency of substance use disorders.

Background: ALCOHOL DEPENDENCE IS EXTREMELY COMMON IN PATIENTS WITH BIPOLAR DISORDER AND IS ASSOCIATED WITH UNFAVORABLE OUTCOMES INCLUDING TREATMENT NONADHERENCE, VIOLENCE, INCREASED HOSPITALIZATION, AND DECREASED QUALITY OF LIFE. While naltrexone is a standard treatment for alcohol dependence, no controlled trials have examined its use in patients with co-morbid bipolar disorder and alcohol dependence. In this pilot study, the efficacy of naltrexone in reducing alcohol use and on mood symptoms was assessed in bipolar disorder and alcohol dependence.

Methods: Fifty adult outpatients with bipolar I or II disorders and current alcohol dependence with active alcohol use were randomized to 12 weeks of naltrexone (50 mg/d) add-on therapy or placebo. Both groups received manual-driven cognitive behavioral therapy designed for patients with bipolar disorder and substance-use disorders. Drinking days and heavy drinking days, alcohol craving, liver enzymes, and manic and depressed mood symptoms were assessed.

Results: The 2 groups were similar in baseline and demographic characteristics. Naltrexone showed trends ($p < 0.10$) toward **A GREATER DECREASE IN DRINKING DAYS** (binary outcome), **ALCOHOL CRAVING, AND SOME LIVER ENZYME LEVELS THAN PLACEBO.** Side effects were similar in the 2 groups. Response to naltrexone was significantly related to medication adherence.

Conclusions: RESULTS SUGGEST THE POTENTIAL VALUE AND ACCEPTABLE TOLERABILITY OF NALTREXONE FOR ALCOHOL DEPENDENCE IN BIPOLAR DISORDER PATIENTS. A larger trial is needed to establish efficacy.

7. [Findings on Alcohol Dependence Point to Promising Avenues for Targeted Therapies](#)

Kuehn BM. JAMA, 04/22/09

Comment: This is a “Medical News and Perspective” article from the prestigious Journal of the American Medical Association. It is worth reading the complete article to get a sense of how current research is focused on finding ways to reduce craving and relapse. Contact me if you’d like a copy of the article. Send an email request to pcohen@dhmh.state.md.us.

Scientists are identifying various genetic and biologic pathways underlying alcohol dependence in individuals and developing treatments to target these pathways.

Clinicians have long recognized important differences among patients with alcohol dependence. Now scientists are working to translate these observations into therapies that will target the genetic and biological underpinnings of various types of alcohol use disorders.

For example, growing evidence indicates that patients with alcohol dependence who carry a particular variant of an opioid receptor gene are more likely to respond to naltrexone, raising the possibility that genetic tests may one day guide medication selection. Other evidence from preclinical and preliminary clinical studies points to potential alternative therapies for patients with alcoholism who are very sensitive to stress. And animal and preliminary human studies suggest that the smoking cessation drug varenicline may aid patients with alcohol use disorders.

8. [Anticonvulsant drugs in cocaine dependence: A systematic review and meta-analysis](#)

Alvarez Y et al. Journal of Substance Abuse Treatment, 09/04/09

Comment: Here’s another probable dead end for treating cocaine dependence with medications.

A systematic review and meta-analysis according to the methodology developed by the Cochrane Collaboration and the Quality of Reporting of Meta-Analyses statement based on randomized controlled trials to evaluate the efficacy of anticonvulsants in subjects with cocaine dependence were performed. Fifteen randomized, double-blind, placebo-controlled clinical trials involving 1,236 patients were included. Two outcome measures were evaluated: retention in the anticonvulsant treatment (compared to the placebo treatment) and the subsequent cocaine use, measured by urinalysis results. The efficacy of the seven anticonvulsant drugs analyzed was not homogenous. On average, 50% of the enrolled participants were lost to follow-up. Treatments did not show an improvement in subject retention compared to placebo. Overall, the number of cocaine-positive urine samples was close to statistical significance (95% confidence interval =

0.85–1.06) compared to placebo. Available clinical trials indicate that **THERE IS INSUFFICIENT EVIDENCE TO JUSTIFY THE USE OF ANTICONVULSANT DRUGS IN TREATING COCAINE DEPENDENCE.**

9. [Cancer Incidence among Patients with Alcohol Use Disorders—Long-Term Follow-Up](#)

Thygesen LC et al. Alcohol and Alcoholism , 06/11/09

Comment: This large scale study in Denmark gives us a good reason for why we help people recover, if only to reduce the rates of cancer and the pain and heartache of dying from these cruel diseases.

Aims: The aim of this study was to compare the cancer morbidity in a large cohort of patients with alcohol use disorders in the general Danish population.

Methods: We included 15,258 men and 3552 women free of cancer when attending the Copenhagen Outpatient Clinic for Alcoholics in the period from 1954 to 1992. The cancer incidence until 1999 of the patients and the general Danish population was obtained through linkage with the Danish Cancer Registry. The incidence rates were standardized (SIR) according to sex, age and calendar time.

Results: A total of 2145 men developed cancer compared to 1140.8 expected cases (SIR = 1.9; 95% confidence interval (CI) 1.8–2.0), while 601 women developed cancer compared to 239.1 expected cases (SIR = 2.5; 95% CI 2.3–2.7). Highly significant and strongly elevated incidence rates were found for cancer of the tongue, mouth, pharynx, oesophagus, liver, larynx and lung. A higher incidence rate was seen for renal cancer for both men (1.4; 1.1–1.8) and women (2.1; 1.0–3.8). The incidence of breast cancer in women was non-significantly elevated, but significantly elevated incidence rate was found for cervical cancer (1.8; 1.2–2.6). We did not observe increased incidence of colon, rectal or urinary bladder cancer.

Conclusions: In conclusion, this study confirms **THE WELL-ESTABLISHED ASSOCIATION BETWEEN HIGH ALCOHOL INTAKE AND CANCER OF THE UPPER DIGESTIVE TRACT AND LIVER.** In addition, the results indicate **A SIGNIFICANTLY ELEVATED OCCURRENCE OF RENAL CANCER, BUT NOT OF BREAST CANCER AND COLORECTAL CANCER,** in patients with alcohol use disorders.

10. [Acupuncture for Alcohol Dependence: A Systematic Review](#)

Cho SH et al. Alcoholism, 05/05/09

Comment: It is extremely difficult to do research on the benefits of acupuncture. NIH is sponsoring grants to develop the tools for evaluating alternative treatments such as acupuncture or for studying Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence. Go to this website to see what the National Center for Complementary and Alternative Medicine (NCCAM) is funding: <http://www.nccam.nih.gov/>. You might find a research study for the people you help, that gives free treatment.

Background: Acupuncture has been used in the treatment of substance-related disorders for the past 30 years. However, a systematic review to assess the effect of various types of acupuncture for alcohol dependence has not yet been performed. The present systematic review assessed the results of randomized controlled trials (RCTs).

Methods: Nineteen electronic databases, including English, Korean, Japanese, and Chinese databases, were systematically searched for RCTs of acupuncture for alcohol dependence up to June 2008 with no language restrictions. The methodological qualities of eligible studies were assessed using the criteria described in the Cochrane Handbook.

Results: Eleven studies, which comprised a total of 1,110 individual cases, were systematically reviewed. Only 2 of 11 trials reported satisfactorily all quality criteria. Four trials comparing acupuncture treatment and sham treatments reported data for alcohol craving. Three studies reported that there were no significant differences. Among 4 trials comparing acupuncture and no acupuncture with conventional therapies, 3 reported significant reductions. No differences between acupuncture and sham treatments were found for completion rates (Risk Ratio = 1.07, 95% confidence interval, CI = 0.91 to 1.25) or acupuncture and no acupuncture (Risk Ratio = 1.15, 95% CI = 0.79 to 1.67). Only 3 RCTs reported acupuncture-related adverse events, which were mostly minimal.

Conclusions: **THE RESULTS OF THE INCLUDED STUDIES WERE EQUIVOCAL,** and the poor methodological quality and the limited number of the trials **DO NOT ALLOW ANY CONCLUSION ABOUT THE EFFICACY OF ACUPUNCTURE FOR TREATMENT OF ALCOHOL DEPENDENCE.** More research and well-designed, rigorous, and large clinical trials are necessary to address these issues.

11. [The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers](#)

Walsh SL et al. Drug and Alcohol Dependence, 01/12/09

Comment: In other words, there is little difference in the way these three prescription opioids are abused or which one is preferred over another.

Abuse of prescription opioids has risen precipitously in the United States. Few controlled comparisons of the abuse liability of the most commonly abused opioids have been conducted. This outpatient study employed a double-blind, randomized, within-subject, placebo-controlled design to examine the relative abuse potential and potency of oral oxycodone (10, 20 and 40 mg), hydrocodone (15, 30 and 45 mg), hydromorphone (10, 17.5 and 25 mg) and placebo. Healthy adult volunteers ($n = 9$) with sporadic prescription opioid abuse participated in 11 experimental sessions (6.5 h in duration) conducted in a hospital setting. All three opioids produced a typical *mu* opioid agonist profile of subjective (increased ratings of liking, good effects, high and opiate symptoms), observer-rated, and physiological effects (miosis, modest respiratory depression, exophoria and decrements in visual threshold discrimination) that were generally dose-related. Valid relative potency assays revealed that oxycodone was roughly equipotent to or slightly more potent than hydrocodone. Hydromorphone was

only modestly more potent (less than two-fold) than either hydrocodone or oxycodone, which is inconsistent with prior estimates arising from analgesic studies.

THESE DATA SUGGEST THAT THE ABUSE LIABILITY PROFILE AND RELATIVE POTENCY OF THESE THREE COMMONLY USED OPIOIDS DO NOT DIFFER SUBSTANTIALLY FROM ONE ANOTHER AND SUGGEST THAT ANALGESIC POTENCIES MAY NOT ACCURATELY REFLECT RELATIVE DIFFERENCES IN ABUSE LIABILITY OF PRESCRIPTION OPIOIDS.

12. [Modafinil for the treatment of cocaine dependence](#)

Anderson AL et al. Drug and Alcohol Dependence, 07/27/09

Comment: And here's another cocaine study, and for good reason.

Modafinil (brand name Prodigil) is prescribed for narcolepsy, obstructive sleep apnea or hypoapnea syndrome, shift work sleep disorder, and multiple sclerosis-related fatigue. There have been some reports of abuse or dependency on this medication; the specific mechanism of action in the brain is not known, as it is for other abusable substances.

For the cocaine user who is not dependent on alcohol, Modafinil can increase the weekly percentage of non-use days from cocaine. For all cocaine users no matter what other chemicals they abuse, it can increase their maximum number of non-use days and can reduce their craving. Please note that this is an expensive medication, costing about \$348 per month.

Aim: Modafinil was tested for efficacy in facilitating abstinence in cocaine-dependent patients, compared to placebo.

Methods: This was a double-blind placebo-controlled study, with 12 weeks of treatment and a 4-week follow-up. Six outpatient substance abuse treatment clinics participated in the study. There were 210 treatment-seekers randomized, having a diagnosis of cocaine dependence; 72 participants were randomized to placebo, 69 to modafinil 200 mg, and 69 to modafinil 400mg, taken once daily on awakening. Participants came to the clinic three times per week for assessments and urine drug screens, and had one hour of individual psychotherapy weekly. The primary outcome measure was the weekly percentage of cocaine non-use days.

Results: The GEE regression analysis showed that for the total sample, there was no significant difference between either modafinil group and placebo in the change in average weekly percent of cocaine non-use days over the 12-week treatment period ($p > 0.79$). However, two secondary outcomes showed significant effects by modafinil 200 mg: the maximum number of consecutive non-use days for cocaine ($p = 0.02$), and a reduction in craving ($p = 0.04$). Also, a *post hoc* analysis showed a significant effect of modafinil that increased the weekly percentage of non-use days in the subgroup of those cocaine patients who did *not* have a history of alcohol dependence ($p < 0.02$).

Conclusions: THESE DATA SUGGEST THAT MODAFINIL, IN COMBINATION WITH INDIVIDUAL BEHAVIORAL THERAPY, WAS EFFECTIVE FOR INCREASING

COCAINE NON-USE DAYS IN PARTICIPANTS WITHOUT CO-MORBID ALCOHOL DEPENDENCE, AND IN REDUCING COCAINE CRAVING.

13. [Psychopathology in Cocaine-abusing Adolescents](#)

Kilgus MD & Pumariega AJ. Addictive Disorders & Their Treatment , 09/10/09

Comment: Finally, an article on adolescents. Dr. Pumariega is a highly respected child and adolescent psychiatrist and a pioneer in the area of developing systems of care. This article confirms what the ADAA data shows: cocaine, as well as opioid use, is associated with a higher frequency of moderate to severe mental health problems, compared to other substance abusing adolescents.

Objective: Cocaine is a widely abused drug in the United States and a significant, but not well studied, problem in adolescent populations. Few studies have used structured diagnostic interviews and Diagnostic and Statistical Manual for Mental Disorders criteria to examine comorbidity in adolescents referred to inpatient treatment for substance use disorders (SUDs). Many psychiatric disorders have their onset and develop during adolescence, and a complex overlap can develop between substance abuse and adolescent behavioral or emotional disturbances. This study investigates co-occurring psychiatric disorders in cocaine-dependent adolescents.

Method: Subjects were adolescents aged 14 to 17 years who had abused cocaine and were attending the 6-week adolescent inpatient drug and alcohol treatment program for the South Carolina Department of Mental Health. They completed the Diagnostic Interview Schedule for Children 2.3, PC version before viewing a 36-minute videotape with salient cocaine cues for craving.

Results: Of the 31 subjects completing the study, 21 (68%) subjects were diagnosed with an axis I diagnosis other than conduct or other SUDs.

Conclusions: The prevalence of affective disorders including sex differences is similar to other investigated adolescent SUD populations. However, **COCAINE-PREFERRING ADOLESCENTS MAY HAVE HIGHER COMORBIDITY AND MORE ANXIETY DISORDERS. THE PRESENCE OF ANXIETY MAY BE A MAJOR FACTOR IN ADOLESCENT COCAINE ADDICTION.**

14. [Basic neuroanatomy and neuropharmacology of cannabinoids](#)

Breivogel CS et al. International Review of Psychiatry, 04/21/09

Comment: This is “The Second Most Off-Putting Title of 2009” but stay with it. In plain English, we have cannabis receptors in our brains and substances in our bodies that are similar to cannabis (cannabinoids). This is also true for the fact that the brain and body has opioid brain receptors and opiate like substances (endorphins).

In some of the mental disorders, these cannabinoids are disrupted and may be one of the causes for a disorder. Future research will focus on how to manipulate

this cannabinoid system to see if it can help treat mental disorders. This research may also provide some clue to why marijuana is the number one drug of choice by kids who have ADHD, for example.

Humans have used *Cannabis sativa* (marijuana) for at least 12,000 years, but researchers have only recently described an endogenous cannabinoid system. The endocannabinoid system modulates an array of physiological and psychological functions. Endocannabinoids are widely distributed throughout the body, including the central nervous system (CNS). This article gives a basic overview of endocannabinoid neuroanatomy and function. Several endocannabinoids have been discovered to date, and their roles are being elucidated. Two G-protein coupled cannabinoid receptors, CB1R and CB2R, have been identified, although other candidate receptors exist, including ion channel and nuclear receptors that might be components of the endocannabinoid system. It appears that cannabinoids are dysregulated in a number of psychiatric disorders and might be involved in their pathogenesis. There is now evidence that manipulation of the endocannabinoid system could be a therapeutic target for a variety of conditions.

15. [Does Cannabis Use Affect Treatment Outcome in Bipolar Disorder?: A Longitudinal Analysis](#)

Van RI et al. The Journal of Nervous and Mental Disease, 02/06/09

Comment: So does it? Yes, when it comes to 1) less compliance, 2) more overall illness severity, mania, and psychosis, 3) less satisfaction with life, and 4) a lower probability of having a relationship. This research examines the effects of cannabis on a very large group of bipolar patients over 1 year.

This research points the way to our using motivational interviewing. We can help the person achieve his or her positive goals while pointing out a) the discrepancies in what the person wants and b) how pot prevents them from getting what he or she wants.

Research suggests that cannabis use affects negatively on onset and outcome of schizophrenia, but less is known about possible effects in mood disorders. Bipolar in- and outpatients ($N = 3459$) were enrolled in an observational study. The influence of cannabis exposure on clinical and social treatment outcome measures was examined over the course of 1 year, as well as the effects on these associations of third mediating variables. Over 12 months of treatment, **CANNABIS USERS EXHIBITED LESS COMPLIANCE AND HIGHER LEVELS OF OVERALL ILLNESS SEVERITY, MANIA, AND PSYCHOSIS COMPARED WITH NONUSERS.** Additionally, cannabis users experienced **LESS SATISFACTION WITH LIFE AND** had **A LOWER PROBABILITY OF HAVING A RELATIONSHIP** compared with nonusers. There was little evidence that cannabis-outcome associations were mediated by third variables. An independent impact of cannabis use on psychopathologic outcomes in patients with bipolar disorder was apparent, whereas the impact on social outcomes was modest.

16. [Opioid abuse in pain patients – psychological aspects and treatment](#)

Gronbladh L. Scandinavian Journal of Pain, 09/01/09

Comment: This title of this journal might strike you as funny. This is not a journal of pain but a journal about pain. Unless you think that Scandinavians cause too much pain. Not if you are an ABBA fan like me.

This Swedish hospital initiated a thoughtful and effective response to a public health problem. An important message is that attention must be paid in a well-coordinated way to a group of pain patients of whom 68% had a pre-existing psychiatric problem and 32% had pre-existing addictive problems. For your information, the meaning of iatrogenic is “resulting from the activity of physicians; said of any adverse condition in a patient resulting from treatment by a physician or surgeon.” Yes, by prescribing pain meds for even bona fide reasons, the curse can be worse than the cure. That is why it is so important to work closely with a doc who is helping your patient cope with pain to determine when a pain med is medically necessary and when other non-medicine alternatives are shown to work.

Background: Iatrogenic opioid addiction among chronic pain patients was the initiative for starting a structured, comprehensive methadone program for pain patients at the University hospital of Uppsala. Some patients with chronic non-malignant pain are prescribed large doses of short acting opioids for parental use or for intravenous self-administration at home. Doses escalate, tolerance develops, side effects emerge and the need of professional health care is high and to high costs. In spite of this, pain relief is poor. The patient and the doctor start to lose control of the situation. Also diversion of legally prescribed short-acting opioids in high doses occurs. To meet this iatrogenic opioid addiction we used the concept of a comprehensive methadone program.

Aim: The aims were to improve pain relief and quality of life in pain patients with problematic opioid use and to investigate background factors explaining problems with opioid use and dependence. The aim was also to minimise side effects, stop dose escalation and reduce tolerance development as well as to limit diversion through safe dispensing.

Method: Each patient accepted in the methadone program was evaluated of somatic diseases and classified of pain mechanism as well as type of dependence, physical, psychological and substance abuse history. The inclusion criteria were: Age over 20, severe non-malignant pain, dependence of opioids for more than one year and insufficient pain control. The switch to per oral methadone mixture was done as an inpatient procedure over 2-6 weeks. Doses of methadone would be gradually increased as short-acting opioids were slowly tapered in cooperation with the patient to minimise severe pain and abstinence symptoms. The established dose could be dispensed as needed to one, two or three daily doses. Before discharge a treatment plan was set up to optimise the quality of life. For patients in risk of drug abuse, urine samples are collected weekly. In this program we have included two treatment philosophies, a highly

structured one followed by an adaptive philosophy. This two-phase approach appears to be compatible with high acceptance by our pain patients.

Material: 60 patients (29 female) in ages ranging from 26 to 68 years were included. Medical records and psychosocial investigation of all patients were studied for pain problems, duration of pain mechanism, psychiatric co-morbidity and maximum of daily doses of opioids before methadone treatment was introduced.

Results: All subjects were suffering from severe pain and low quality of life including problems of opioid dependence. 41 (68%) had a background of psychiatric problems often pre-existent to the pain disorder. An important finding was that 19 (32%) of subjects had addiction problems before debut of the pain disorder. At the end of study 42 patients are still in the program. Of the 48 evaluated patients 36 (75%) regarded pain relief as good and 12 (25%) as moderate.

Conclusion: AN ORAL COMPREHENSIVE METHADONE TREATMENT MODEL CAN BE USED TO SUCCESSFULLY TREAT PATIENTS WITH COMPLEX PAIN SYNDROMES AND OPIOID DEPENDENCE.

17. [The Adolescent Substance Abuse Prevention Study: A randomized field trial of a universal substance abuse prevention program](#)

Sloboda Z et al. Drug and Alcohol Dependence, 05/07/09

Comment: Research can point to the truth better than common sense can. This Ohio-based Take Charge of Your Life program had originated out of the DARE program. It shows that such an approach might be helpful for baseline marijuana users, but shouldn't be used universally. In fact, DARE may have made matters worse for non-users. But most of us already knew that.

Objectives

The purpose of the study was to determine whether a universal school-based substance abuse prevention program, *Take Charge of Your Life (TCYL)*, prevents or reduces the use of tobacco, alcohol, or marijuana.

Methods

Eighty-three school clusters (representing school districts) from six metropolitan areas were randomized to treatment (41) or control (42) conditions. Using active consenting procedures, 19,529 seventh graders were enrolled in the 5-year study. Self-administered surveys were completed by the students annually. Trained Drug Abuse Resistance Education (D.A.R.E.) police officers presented *TCYL* in seventh and ninth grades in treatment schools. Analyses were conducted with data from 17,320 students who completed a baseline survey. Intervention outcomes were measured using self-reported past-month and past-year use of tobacco, alcohol, and marijuana when students were in the 11th grade.

Results

Main effect analyses show a negative program effect for use of alcohol and cigarettes and no effect for marijuana use. Subgroup analyses indicated that the negative effect occurred among nonusers at baseline, and mostly among white students of both genders. A positive program effect was found for students who used marijuana at

baseline. Two complementary papers explore the relationship of the targeted program mediators to the use of alcohol, tobacco, and marijuana and specifically for students who were substance-free or who used substances at baseline.

Conclusions

THE NEGATIVE IMPACT OF THE PROGRAM ON BASELINE NONUSERS OF ALCOHOL AND TOBACCO INDICATE THAT TCYL SHOULD NOT BE DELIVERED AS A UNIVERSAL PREVENTION INTERVENTION. The finding of a beneficial effect for baseline marijuana users further supports this conclusion. The programmatic and methodological challenges faced by the Adolescent Substance Abuse Prevention Study (ASAPS) and lessons learned offer insights for prevention researchers who will be designing similar randomized field trials in the future.

18. [Varenicline for smoking cessation: A placebo-controlled, randomized study](#)

Wang C et al. *Respirology*, 02/24/09

Comment: We have to do much better in the coming year to focus on smoking in terms of motivating our patients and providing effective treatment, most of all for the women of child-bearing age (see the next abstract 19). As for the medication side of treatment, Varenicline (Chantrix) is expensive but effective, as long as you are monitoring for depressive and suicidal symptoms. In this study that is true even in the Far East.

Background and objective: Varenicline tartrate, a novel, selective, nicotinic acetylcholine receptor partial agonist, has been developed specifically as a smoking cessation drug. This study evaluated the efficacy of a standard regimen of varenicline compared with placebo for smoking cessation in 333 subjects in China, Singapore and Thailand.

Methods: This 24-week, randomized, double-blind, placebo-controlled trial of varenicline, 1 mg bd, consisted of a 12-week treatment period followed by a 12-week non-treatment follow-up period. The primary study end-point was the 4-week continuous abstinence rate defined as the proportion of subjects who reported total abstinence from smoking and other nicotine products from weeks 9–12. A key secondary end-point was the continuous abstinence rate from weeks 9–24, defined as the proportion of subjects who achieved the primary end-point as well as total abstinence from all tobacco products from weeks 13–24.

Results: Both end-points were achieved by a significantly higher proportion of subjects in the varenicline group than in the placebo group. The 4-week continuous abstinence end-point was achieved by 50.3% and 31.6% in the varenicline and placebo groups, respectively ($P = 0.0003$), while continuous abstinence from weeks 9–24 was achieved by 38.2% and 25.0% of subjects, respectively ($P = 0.0080$). The treatment effect was generalizable by treatment centre and country. Varenicline was safe and appeared to be well tolerated by most subjects.

Conclusion: Varenicline was significantly more efficacious for smoking cessation than placebo over a 12-week treatment period and a further 12-week non-treatment follow-up

period in smokers from China, Singapore and Thailand. No significant side-effects were noted.

19. [Developmental consequences of prenatal tobacco exposure](#)

Cornelius MD et al. Current Opinion in Neurology, 03/25/09

Comment: And while we're at it, it's time to focus on another very vulnerable group: mothers in recovery who smoke and their fetuses who are been exposed to tobacco. The developmental effects are striking and do not give the child a healthy start to life.

Purpose of review: This paper reviews results from published, in press, and conference proceedings from 2007 and 2008 that link in-utero tobacco exposure to neurodevelopmental outcomes in exposed offspring.

Recent findings: PRENATAL TOBACCO EXPOSURE (PTE) AFFECTED SPEECH PROCESSING, LEVELS OF IRRITABILITY AND HYPERTONICITY, ATTENTION LEVELS, ABILITY TO SELF-REGULATE, NEED TO BE HANDLED, AND RESPONSE TO NOVELTY PREFERENCE IN INFANTS. IN EARLY CHILDHOOD, PTE EFFECTS WERE MOSTLY BEHAVIORAL OUTCOMES INCLUDING ACTIVITY AND INATTENTION AND EXTERNALIZING BEHAVIORS, INCLUDING CONDUCT DISORDER AND ANTISOCIAL BEHAVIOR. IN ADOLESCENTS, PTE PREDICTED INCREASED ATTENTION DEFICIT HYPERACTIVITY DISORDER, MODULATION OF THE CEREBRAL CORTEX AND WHITE MATTER STRUCTURE, AND NICOTINE ADDICTION. Several studies found moderating effects with PTE and genetic susceptibilities including dopamine transporter, serotonergic synaptic function, and monamine oxidase pathways. Other studies suggested that environmental and genetic factors might be more important than the direct teratological effects of PTE.

Summary: The majority of studies reviewed were prospective and tobacco exposure was quantified biologically. Most demonstrated a direct association between PTE and neurodevelopmental outcomes. More work is needed to examine multifactorial influences. Effects of PTE on the offspring appear to be moderated by genetic variability, neurobehavioral disinhibition, and sex.

20. [Adolescent smoking and depression: evidence for self-medication and peer smoking mediation](#)

Audrain-McGovern J et al. Addiction, 09/18/09

Comment: The language is a bit thick here. Put simply, this research states that depression in the middle teenager can predict the progression of smoking and having more smoking peers. By late adolescence the depressive symptoms begin to reduce. In other words, it's possible that teen depression gets you to start smoking, in part because it is reinforced by hanging around other smoking

peers. But then you're hooked with a serious health problems, even if you stop being so depressed.

Aims: The nature of the relationship between adolescent smoking and depression is unclear and the mechanisms that account for the comorbidity have received little investigation. The present study sought to clarify the temporal precedence for smoking and depression and to determine whether these variables are linked indirectly through peer smoking.

Participants: The sample was composed of 1093 adolescents participating in a longitudinal study of the behavioral predictors of smoking adoption.

Design and measurements: In this prospective cohort study, smoking, depression, peer smoking and other covariates were measured annually from mid-adolescence (9th grade; age 14) to late adolescence (12th grade, age 18).

Findings: Parallel processes latent growth curve models supported a bidirectional relationship between adolescent smoking and depression, where **HIGHER DEPRESSION SYMPTOMS IN MID-ADOLESCENCE (AGE 14) PREDICTED ADOLESCENT SMOKING PROGRESSION FROM MID- TO LATE ADOLESCENCE (AGES 14-18)**. A significant indirect effect indicated that **HIGHER DEPRESSION SYMPTOMS ACROSS TIME PREDICTED AN INCREASE IN THE NUMBER OF SMOKING PEERS, WHICH IN TURN PREDICTED SMOKING PROGRESSION FROM MID-ADOLESCENCE TO LATE ADOLESCENCE**. IN ADDITION, **SMOKING PROGRESSION PREDICTED A DECELERATION OF DEPRESSION SYMPTOMS FROM MID- TO LATE ADOLESCENCE**. A significant indirect effect indicated that greater smoking at baseline predicted a deceleration in the number of smoking peers across time, which predicted a deceleration in depression symptoms from mid-adolescence to late adolescence.

Conclusions: The current study provides the first evidence of bidirectional self-medication processes in the relationship between adolescent smoking and depression and highlights peer smoking as one explanation for the comorbidity.

Thanks for reading through these studies. Every quarter, I'll keep you up to date with the latest information.