We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html

Guideline CPD

Canadian guideline for the clinical management of high-risk drinking and alcohol use disorder

Evan Wood MD PhD, Jessica Bright MPH, Katrina Hsu MSc, Nirupa Goel PhD, Josey W.G. Ross MA, Averill Hanson RSW MPH, Rand Teed BEd, Ginette Poulin RD MD, Bryany Denning MSc MSW, Kim Corace PhD C.Psych, Corrina Chase MA, Katelyn Halpape PharmD, Ronald Lim MD, Tim Kealey BAdmin, Jürgen Rehm PhD; for the Canadian Alcohol Use Disorder Guideline Committee

Cite as: *CMAJ* 2023 October 16;195:E1364-79. doi: 10.1503/cmaj.230715

See related article at www.cmaj.ca/lookup/doi/10.1503/cmaj.231015

Background: In Canada, low awareness of evidence-based interventions for the clinical management of alcohol use disorder exists among health care providers and people who could benefit from care. To address this gap, the Canadian Research Initiative in Substance Misuse convened a national committee to develop a guideline for the clinical management of high-risk drinking and alcohol use disorder.

Methods: Development of this guideline followed the ADAPTE process, building upon the 2019 British Columbia provincial guideline for alcohol use disorder. A national guideline committee (consisting of 36 members with diverse expertise, including academics, clinicians, people with lived and living experiences of alcohol use, and people who self-identified as Indigenous or Métis) selected priority topics, reviewed evidence and reached consensus on the recommendations. We used the Appraisal of Guidelines for Research and Evaluation Instrument (AGREE II) and the Guidelines International Network's Principles for Disclosure of Interests and Management of Conflicts to ensure the guideline met international standards for transparency, high quality and methodological rigour. We rated the final recommendations using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool; the recommendations underwent external review by 13 national and international experts and stakeholders.

Recommendations: The guideline includes 15 recommendations that cover screening, diagnosis, withdrawal management and ongoing treatment, including psychosocial treatment interventions, pharmacotherapies and community-based programs. The guideline committee identified a need to emphasize both underused interventions that may be beneficial and common prescribing and other practice patterns that are not evidence based and that may potentially worsen alcohol use outcomes.

Interpretation: The guideline is intended to be a resource for physicians, policymakers and other clinical and nonclinical personnel, as well as individuals, families and communities affected by alcohol use. The recommendations seek to provide a framework for addressing a large burden of unmet treatment and care needs for alcohol use disorder within Canada in an evidence-based manner.

Data from the 2021 Canadian Community Health Survey indicate that about 18% of people aged 15 years or older in Canada meet the clinical criteria for an alcohol use disorder (AUD) in their lifetime.[1] Over 50% of people in Canada aged 15 years or older currently drink more than the amount recommended in *Canada's Guidance on Alcohol and Health*, issued in 2023.[2]

Alcohol consumption in Canada is markedly higher than the global average and above the median for high-income countries.[3] In 2016, more than 4% of all deaths were attributed to alcohol use; alcohol use also contributed to more than 6% of all potential years of life lost for individuals aged 15 years and older in Canada.[4] Additionally, alcohol use and AUD represent major contributions to ill health in Canada, with research suggesting that more than 200 health consequences, including injuries and fatalities, are attributable to alcohol use.[5]

However, evidence-informed interventions for AUD have not been widely implemented in Canada,[6] likely owing to structural problems such as stigma and lack of health care provider training,[7] compounded by a lack of national evidence-based guidelines. Although national statistics are lacking, studies from Canadian provinces have shown that less than 2% of eligible patients receive evidence-based alcohol pharmacotherapies.[8,9] Additionally, high-risk drinking and AUD are often unrecognized and underdiagnosed in the health care system.[9] As a result, people

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CRISM

Financial contribution:

Health Canada Santé Canada

Presenter Disclosure: Evan Wood

- **Relationships with financial sponsors:**
  - **Professor of medicine at UBC where salary is supported by a Tier 1 Canada Research Chair in Addiction Medicine funded by CIHR.**
  - **Salary and consulting support is also provided by the US National Institutes of Health through the US National Institute on Drug Abuse (NIDA)**
  - **Practice includes the care of persons with substance use disorder through Vancouver Coastal Health as well as a private practice providing occupational addiction medicine evaluations**
  - **I have provided legal expertise in cases involving substance use disorder including for the CMPA and trade unions**
  - **I have previously served as an employee and consultant to Numinus Wellness a mental health company**

Mitigating Potential Bias

- The ***Guidelines International Network's Principals for Disclosure of Interests and Management of Conflicts*** were used to ensure the guidelines met international standards for transparency, high quality and methodological rigour
- In today's talk, it should be appreciated that I was co-chair of the guideline that itself represents a conflict though the presentation today is based on my own views

HUMILITY

Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true.

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but, unfortunately, there is a widespread notion that medical research articles

It can be proven that most claimed research findings are false.

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α. Assuming that c relationships are being probed in the field, the expected values of the 2×2 table are given in Table 1. After a research finding has been claimed based on

Learning Objectives

- Demonstrate increased awareness of evidence-based interventions for the clinical management of AUD
- Understand the difference between evidence-based and common non-evidence-based interventions
- Will be focussing on an EBM and a “what I would want to know” perspective rather than other perspectives

Overview of clinical pathway

ASK ABOUT ALCOHOL

"Would it be all right for us to talk about your relationship with alcohol?"

- Asking permission builds trust and comfort

SCREENING AND DIAGNOSIS

"In the past year, how often have you had more than 4 drinks (females) or 5 drinks (males) on any 1 occasion?"

- If 1 occasion or more, ask further screening questions (AUDIT-C*)
- For moderate risk of AUD: Provide brief advice on the health risks and suggestions on how to cut back
- For high risk of AUD: Diagnose using DSM-5-TR criteria

ASSESS THEIR GOALS

If moderate or severe AUD, use brief intervention to discuss goals and a tailored plan:

- Stop drinking
- Cut back on drinking
- Reduce harms of drinking

WITHDRAWAL MANAGEMENT

Use PAWSS* and withdrawal history to determine if low or high risk of severe complications (e.g., delirium tremens, seizures):

- Low risk: outpatient; Rx gabapentin, clonidine
- High risk: inpatient; Rx short course of benzodiazepines

LONG-TERM TREATMENT

- Medications: (1st line) Rx naltrexone or acamprosate; avoid SSRIs,* antipsychotics and long-term benzodiazepines
- Psychosocial treatments: Cognitive behavioural therapy, family-based therapy
- Community supports: Supportive recovery programs, peer groups, etc.

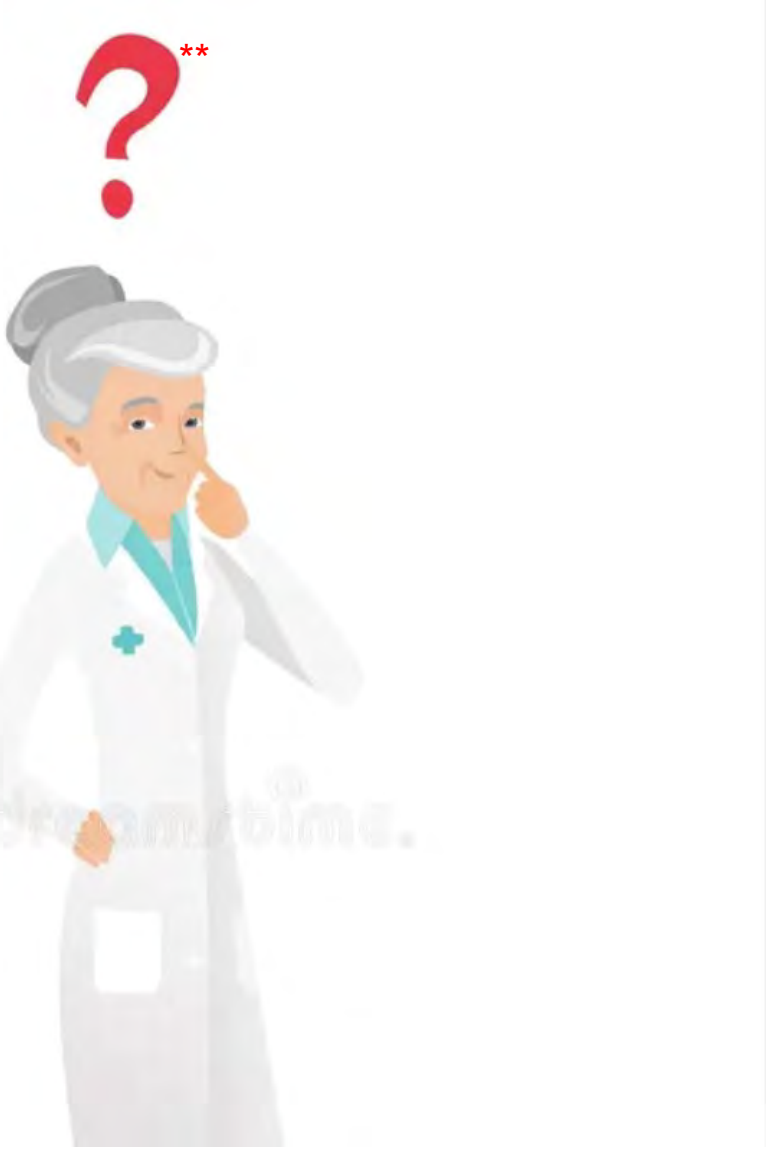
Naltrexone (reduction of heavy drinking)

Acamprosate (Abstinence)

“What about all the other medications commonly prescribed?”

Table 2: Summary of recommendations

	Recommendation	Strength of recommendation*	Certainty of evidence[15]
12	Adult and youth patients should not be prescribed antipsychotics or SSRI antidepressants for the treatment of AUD.	Strong	Moderate
13	Prescribing SSRI antidepressants is not recommended for adult and youth patients with AUD and a concurrent anxiety or depressive disorder. **	Strong	Moderate



ORIGINAL PAPER

Cynthia A. Beck · Scott B. Patten · Jeanne V. A. Williams · Jian Li Wang · Shawn R. Currie
Colleen J. Maxwell · Nady El-Guebaly

Antidepressant utilization in Canada

Accepted: 22 June 2005 / Published online: 27 September 2005

Abstract *Objective* Antidepressant utilization can be used as an indicator of appropriate treatment for major depression. The objective of this study was to characterize antidepressant utilization in Canada, including the relationships of antidepressant use with sociodemographic variables, past-year and lifetime depression, number of past depressive episodes, and other possible indications for antidepressants. *Method* We examined data from the Canadian Community Health Survey (CCHS) Cycle 1.2. The CCHS was a nationally representative mental health survey (N= 36,984) conducted in 2002 that included a diagnostic instrument for past-year and lifetime major depressive episodes and other psychiatric disorders and a record of past-year antidepressant use. *Results* Overall, 5.8% of Canadians were taking antidepressants, higher than the annual prevalence of major depressive episode (4.8%) in the survey. Among persons with a past-year major depressive episode, the frequency of antidepressant use was 40.4%. After application of adjustments for probable successful outcomes of treatment, the estimated frequency of antidepressant use for major depression was more than 50%. Frequency of antidepressant treatment among those with a history of depression but without a past-year episode increased with the number of previous episodes. Among those taking antidepressants over the past year, only 33.1% had had a past-year episode of major depression. Migraine, fibromyalgia, anxiety disorder, or past depression was present in more than 60% of those taking antidepressants without a past-year episode of depression. *Conclusions* The CCHS results suggest that antidepressant use has increased substantially since the early 1990s, and also that these medications are employed extensively for indications other than depression.

Key words antidepressive agents – drug utilization – major depressive disorder – epidemiology – Canada – health surveys

This research was presented at the Canadian Academy for Psychiatric Epidemiology 2004 Annual Scientific Symposium on October 14, 2004 in Montreal, Canada.

Disclaimer: this research and analysis were based on data from Statistics Canada. The opinions expressed in this paper do not represent the views of Statistics Canada.

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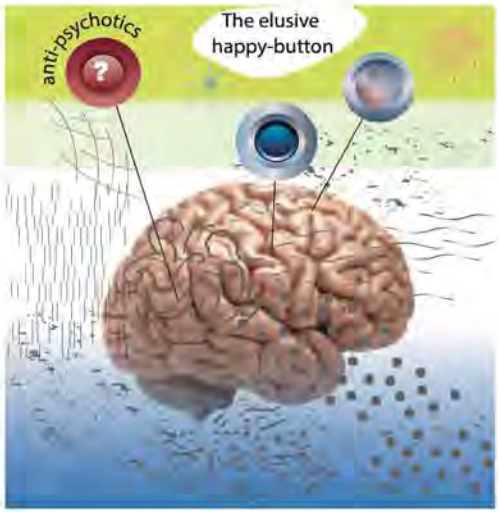
THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Antipsychotics should not be used for non-psychotic depression

This Letter reviews clinical evidence for use of antipsychotics for depression. In Canada, two antipsychotic drugs are approved to treat major depressive disorder (MDD) that is not responsive to other treatment. Quetiapine (Seroquel XR) is approved as monotherapy or in combination with conventional antidepressants for symptomatic relief of MDD "when currently available approved antidepressant drugs have failed".[1] Aripiprazole (Abilify) is approved only for adjunctive treatment of adults with "inadequate response to prior antidepressant treatments during the current episode".[2] Olanzapine, risperidone, ziprasidone, and amisulpiride (not available in Canada) have also been evaluated in randomized trials for MDD. **This Letter focuses on quetiapine because it is the most studied antipsychotic in this setting.**

Significant persistent depression that impairs quality of life and affects work, social and family functioning is called MDD. At its worst, it can lead to suicide. **The lifetime prevalence of MDD has been estimated in a systematic review at 6.7 per 100 people.**[3] Goals of therapy include amelioration of suffering, suicide prevention and restoration of normal functioning. Maintaining employment, positive social interactions and healthy lifestyle are obvious therapeutic targets, but avoiding drug-induced illness and any deleterious

therapeutics letter
July - August 2015



Pharmacology

The marketing label "atypical (second generation) antipsychotic" camouflages properties shared with older antipsychotics. With the exception of clozapine, all antipsychotics block dopamine (D2) receptors, cause extrapyramidal symptoms and signs, tardive dyskinesia and elevate plasma prolactin. The parent drugs or their active metabolites also antagonize serotonin, histamine and alpha-receptors. Quetiapine's active metabolite, norquetiapine, blocks muscarinic cholinergic receptors, causing dry mouth and other anticholinergic effects.[1]

Drugs of this "class" can induce postural hypotension by blocking alpha receptors. They also cause weight gain, diabetes and hypercholesterolemia. Risperidone, quetiapine and aripipra-

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THERAPEUTICS

therapeutics letter
July - August 2015

ORIGINAL ARTICLES

A Review of the Evidence for the Efficacy and Safety of Trazodone in Insomnia

Wallace B. Mendelson, MD

Published: April 15, 2005

ARTICLE ABSTRACT

OBJECTIVE:

Trazodone, a triazolopyridine antidepressant, is currently the second most commonly prescribed agent for the

Remission of Psychiatric Symptoms Among Drug Misusers After Drug Dependence Treatment

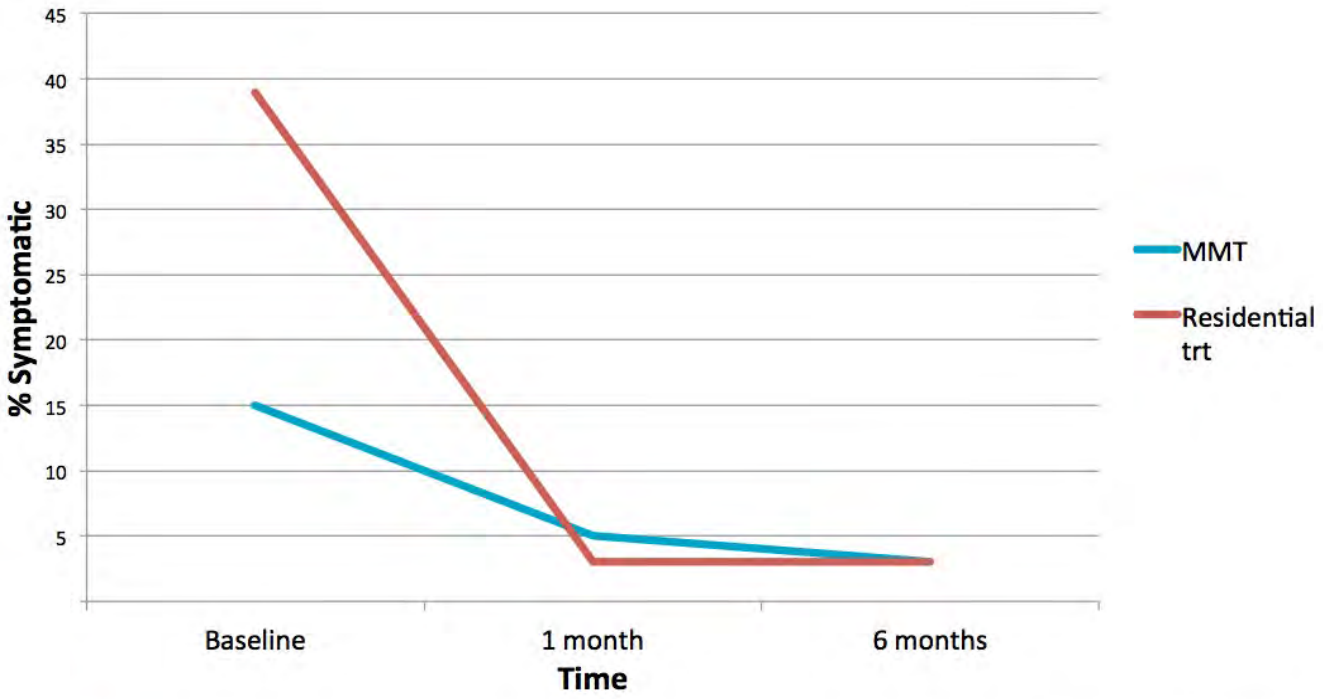
Michael Gossop, PhD, John Marsden, PhD, and Duncan Stewart, PhD

Abstract: The study investigates changes in psychiatric symptoms after drug dependence treatment, and relationships between pretreatment problems, illicit drug use, treatment retention, and changes in psychiatric symptoms. The sample comprised 662 drug-dependent adults recruited at admission to treatment in residential rehabilitation programs (15 agencies) or outpatient methadone treatment (16 methadone maintenance programs and 15 methadone reduction programs). Using a longitudinal, prospective cohort design, data were collected by structured interviews at intake to treatment and at 1-month and

delivery (Dixon et al., 1997; Havassy et al., 2004; Kessler et al., 1999; Schuckit and Hesselbrock, 1994).

A number of studies have reported worse substance use outcomes among patients with comorbid psychiatric disorders (Brown et al., 1998; Compton et al., 2003; Kosten et al., 1986; Rounsaville et al., 1982, 1987). What is less well understood is the precise manner in which substance misuse problems covary with psychiatric disorders. The etiology and relationship of psychiatric disorders with drug dependence are complex. Psychiatric disorders may represent indepen-

Remission of Psychiatric Symptoms with Addictions Treatment



Source: Gossop et al., J Nervous Mental Disease 2006

Several common justifications that contribute to polypharmacy (i.e. what I previously taught)

- Effective pharmacotherapies for concurrent disorders are critical to improve AUD treatment outcomes
- This may be particularly true among poly-substance use users (e.g. nicotine, cannabis, cocaine)
- Medications should be prescribed for a several months as a therapeutic trial given low risk if found to be ineffective
- Combining pharmacotherapy with psychosocial treatments (e.g. relapse prevention training, CBT, etc) is most effective

A Couple of Problems with this with SSRI and Antipsychotics in AUD

1. SSRI and antipsychotics are not particularly effective for treating most mental health symptoms such as depression and anxiety in those with AUD.

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Drug and Alcohol Dependence 78 (2005) 1–22
DRUG and ALCOHOL DEPENDENCE
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Meta-analysis #1

Review

Efficacy of antidepressants in substance use disorders with and without comorbid depression
A systematic review and meta-analysis

Marta Torrens[a,*], Francina Fonseca[a], Gerard Mateu[a], Magí Farré[b]

[a] *Psychiatric and Drug Abuse Department, Hospital del Mar-IAPs, Passeig Marítim 25-29, E-08003 Barcelona, Spain*
[b] *Pharmacology Unit, Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, and Universitat Autònoma de Barcelona, Spain*

Received 18 July 2004; received in revised form 16 September 2004; accepted 26 September 2004

Abstract

Antidepressants are commonly used in substance abusers due to the potential effect on some underlying mechanisms involved in drug use disorders and to treat comorbid depression. A systematic review of the literature of the efficacy of antidepressant drugs in subjects with drug abuse disorders, including alcohol, cocaine, nicotine and opioid, with and without comorbid depression was performed. Only randomised, double-blind, controlled trials have been evaluated. A meta-analysis was done with the included studies that used common evaluation procedures in alcohol, cocaine and opioid dependence. Based on the present review some recommendations may be proposed.

The prescription of antidepressants for drug abuse seems only clear for nicotine dependence with or without previous comorbid depression (bupropion and nortryptiline). In alcohol dependence without comorbid depression, the use of any antidepressant seems not justified, while in cocaine dependence has to be clarified. The use of antidepressants in alcohol, cocaine or opioid dependence with comorbid depression needs more studies in well-defined samples, adequate doses and duration of treatment to be really conclusive. Interestingly, SSRIs do not seem to

Meta-analysis #2

EARLY CAREER PSYCHIATRISTS

Antidepressants for Major Depressive Disorder and Dysthymic Disorder in Patients With Comorbid Alcohol Use Disorders: A Meta-Analysis of Placebo-Controlled Randomized Trials

Nadia Iovieno, MD; Enrico Tedeschini, MD; Kate H. Bentley, BA; A. Eden Evins, MD, MPH; and George I. Papakostas, MD

Objective: Mood and alcohol use disorders are often co-occurring, each condition complicating the course and outcome of the other. The aim of this study was to examine the efficacy of antidepressants in patients with unipolar major depressive disorder (MDD) and/or dysthymic disorder with comorbid alcohol use disorders and to compare antidepressant and placebo response rates between depressed patients with or without comorbid alcohol use disorders.

Data Sources: MEDLINE/PubMed publication databases were searched for randomized, double-blind, placebo-controlled trials of antidepressants used as monotherapy for the acute-phase treatment of MDD and/or dysthymic disorder in patients with or without alcohol use disorders. The search term *placebo* was cross-referenced with each of the antidepressants approved by the US, Canadian, or European Union drug regulatory agencies for the treatment of MDD and/or dysthymic disorder.

Study Selection: 195 articles were found eligible for inclusion in our analysis, 11 of which focused on the treatment of MDD/dysthymic disorder in patients with comorbid alcohol use disorders. The search was limited to articles published between January 1, 1980, and March 15, 2009 (inclusive).

Results: We found that antidepressant therapy was more effective than placebo in patients with comorbid alcohol use disorders (risk ratio of re-

Submitted: *May 4, 2010; accepted September 15, 2010.*
Online ahead of print: *April 19, 2011 (doi:10.4088/JCP.10m06217).*
Corresponding author: *Nadia Iovieno, MD, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, 50 Staniford Street–Suite 401, Boston, MA 02114 (niovieno@partners.org).*

Major depressive disorder (MDD) and dysthymic disorder are highly prevalent and are frequently associated with significant disability, morbidity, and mortality. According to the World Health Organization, MDD has a 12-month prevalence in developed countries between 3.1% and 9.6%,[1] and it contributes to a significant financial, logistical, and psychosocial burden on developed as well as developing nations.[2] Major depressive disorder and dysthymic disorder are often complicated by the co-occurrence of substance use disorders, especially alcohol abuse or dependence. For example, a recent systematic review of studies examining the association between alcohol use disorders and MDD found a median prevalence of current alcohol use disorders of 16% in patients with MDD and a lifetime median prevalence of alcohol use disorders of 30%.[3] More recently, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial found that 24% of patients with MDD also met criteria for a concurrent alcohol use disorder at baseline.[4] The co-occurrence of MDD and alcohol use disorder

PLOS MEDICINE

Meta-analysis #3

RESEARCH ARTICLE

Clinical interventions for adults with comorbid alcohol use and depressive disorders: A systematic review and network meta-analysis

Sean Grant[1,2]*, Gulrez Azhar[2], Eugeniu Han[2], Marika Booth[2], Aneesa Motala[2], Jody Larkin[3], Susanne Hempel[2]

1 Department of Social & Behavioral Sciences, Indiana University Richard M. Fairbanks School of Public Health, Indianapolis, Indiana, United States of America, **2** RAND Corporation, Santa Monica, California, United States of America, **3** RAND Corporation, Pittsburgh, Pennsylvania, United States of America

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Abstract

Background

Meta-analysis #4*

Systematic Review

The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie
2020, Vol. 65(11) 749-769

DOI: 10.1177/0706743720915420
TheCJP.ca | LaRCP.ca
SAGE

Pharmacological Treatment of Mood Disorders and Comorbid Addictions: A Systematic Review and Meta-Analysis

Traitement Pharmacologique des Troubles de L'humeur et des Dépendances Comorbides: Une Revue Systématique et une Méta-Analyse

Paul R. A. Stokes, PhD, FRCPsych[1,2,3], Tahir Jokinen, MBBS, MPhil[1], Sami Amawi, MBBCh, MSc[1], Mutahira Qureshi, MBBS[2], Muhammad Ishrat Husain, MBBS, MD(Res)[4,5], Lakshmi N. Yatham, MBBS, FRCPC[6], John Strang, FRCPsych, FMedSci[3,7], and Allan H. Young, PhD, FRCPsych[1,2,3]

Abstract

Objective: Addiction comorbidity is an important clinical challenge in mood disorders, but the best way of pharmacologically treating people with mood disorders and addictions remains unclear. The aim of this study was to assess the efficacy of pharmacological treatments for mood and addiction symptoms in people with mood disorders and addiction comorbidity.

Methods: A systematic search of placebo-controlled randomized controlled trials investigating the effects of pharmacological treatments in people with bipolar disorder (BD) or major depressive disorder (MDD), and comorbid addictions was performed. Treatment-related effects on mood and addiction measures were assessed in a meta-analysis, which also estimated risks of participant dropout and adverse effects.

Results: A total of 32 studies met systematic review inclusion criteria. Pharmacological therapy was more effective than placebo for improving manic symptoms (standardized mean difference [SMD] = −0.15; 95% confidence interval [95% CI], −0.29 to −0.02; $P = 0.03$) but not BD depressive symptoms (SMD = −0.09; 95% CI, −0.22 to 0.03; $P = 0.15$). Quetiapine significantly improved manic symptoms (SMD = −0.23; 95% CI, −0.39 to −0.06; $P = 0.008$) but not BD depressive symptoms (SMD = −0.07; 95% CI, −0.23 to 0.10; $P = 0.42$). Pharmacological therapy was more effective than placebo for improving depressive symptoms in MDD (SMD = −0.16; 95% CI, −0.30 to −0.03; $P = 0.02$). Imipramine improved MDD depressive symptoms (SMD = −0.58; 95% CI, −1.03 to −0.13; $P = 0.01$) but Selective serotonin reuptake Inhibitors (SSRI)-based treatments had no effect (SMD = −0.06; 95% CI, −0.30 to 0.17; $P = 0.60$). Pharmacological treatment improved the odds of

Meta-analysis #4*

Systematic Review

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Traitement Pharmacologique des Troubles de L'humeur et des Dépendances Comorbides: Une Revue Systématique et une Méta-Analyse

-0.13; $P = 0.01$; $I^2 = 48\%$). Selective serotonin reuptake Inhibitors (SSRI) treatments, either alone or in combination with relapse prevention medications such as naltrexone, had no significant effect on depressive symptoms in people with MDD and comorbid addictions (SSRI-only effect size -0.07; 95% CI, -0.32 to 0.18; $P = 0.58$; $I^2 = 15\%$; SSRI combination

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QUANTITATIVE RESEARCH

Associations of antidepressant use with alcohol use and problem drinking: Ontario population data from 1999 to 2017

Jesus Chavarria[1] · Samantha Wells[1,2,3,4,5] · Tara Elton-Marshall[1,2,4] · Jürgen Rehm[1,2,3,6,7]

Received: 7 October 2020 / Accepted: 31 March 2021 / Published online: 2 June 2021

Abstract

Objective This study investigated the rates of and change in past-year antidepressant use from 1999 to 2017 among a representative sample of Ontario adults and past-year alcohol users and problem drinkers. It examined whether alcohol use and problem drinking are associated with antidepressant use over time, whether gender moderated the effect of problem drinking on antidepressant use, and the potential correlates of past-year antidepressant use.

Method This study utilized data from the Centre for Addiction and Mental Health Monitor study, a repeat cross-sectional telephone survey of the Ontario general adult population. Data are from 15 annual cycles of the survey 1999–2017 (where relevant variables were included), resulting in a sample size of $N = 35{,}210$. Variables of interest included demographic variables, past-year antidepressant use, past-year alcohol use, and past-year problem drinking (e.g., 8+ on the Alcohol Use Disorders Identification Test).

Results Past-year antidepressant use increased from 1999 to 2017 similarly among the full sample, past-year alcohol users, and past-year problem drinkers. Approximately 9% of Ontarians reported past-year antidepressant use in 2017. Overall, past-year problem drinkers were 1.5 times more likely to use antidepressants than non-problem drinkers. Past-year alcohol use was not associated with

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Comparative utilization of pharmacotherapy for alcohol use disorder and other psychiatric disorders among U.S. Veterans Health Administration patients with dual diagnoses

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ABSTRACT

Patients with alcohol use disorder (AUD) and another co-occurring psychiatric disorder are a vulnerable population with high symptom severity. Such patients may benefit from a full arsenal of treatment options including pharmacotherapy. Receipt of AUD pharmacotherapy is generally very low despite recommendations that it be made available to every patient with AUD, including those with co-occurring disorders. Little is known about pharmacotherapy rates for AUD compared to other psychiatric disorders among patients with dual diagnoses. This study compared rates of pharmacotherapy for AUD to those for non-substance use psychiatric disorders and tobacco use disorder among patients with dual diagnoses in the U.S. Veterans Affairs (VA) healthcare system. VA data were used to identify patients with AUD and another psychiatric disorder in fiscal year 2012, and to estimate the proportion receiving pharmacotherapy for AUD and for each comorbid condition. Among subsets of patients with AUD and co-occurring schizophrenic, bipolar, posttraumatic stress or major depressive disorder, receipt of medications for AUD ranged from 7% to 11%, whereas receipt of medications for the comorbid disorder ranged from 69% to 82%. Among patients with AUD and co-occurring tobacco use disorder, 6% received medication for their AUD and 34% for their tobacco use disorder. Among patients with dual diagnoses, rates of pharmacotherapy for AUD were far lower than those for the comorbid disorders and contrary to evidence that medications for AUD are effective. Additional system-wide implementation efforts to identify and address patient- and provider-level barriers are needed to increase AUD pharmacotherapy in this high-need population.

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Pharmacotherapy for anxiety and comorbid alcohol use disorders

Jonathan C Ipser, Don Wilson, Taiwo O Akindipe, Carli Sager, Dan J Stein Authors' declarations of interest

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Collapse all Expand all

Abstract

Available in English | Español | فارسی | 简体中文

Background

Anxiety disorders are a potentially disabling group of disorders that frequently co-occur with alcohol use disorders. Comorbid anxiety and alcohol use disorders are associated with poorer outcomes, and are difficult to treat with standard psychosocial interventions. In addition, improved understanding of the biological basis of the conditions has contributed to a growing interest in the use of medications for the treatment of people with both diagnoses.

Objectives

To assess the effects of pharmacotherapy for treating anxiety in people with comorbid alcohol use disorders, specifically: to provide an estimate of the overall effects of medication in improving treatment response and reducing symptom severity in the treatment of anxiety disorders in people with comorbid alcohol use disorders; to determine whether specific medications are more effective and tolerable than other medications in the treatment of particular anxiety disorders; and to identify which factors (clinical, methodological) predict response to pharmacotherapy for anxiety disorders.

Summary of main results

Evidence collated as part of this review to determine the efficacy of medication in treating anxiety disorder symptoms in people with comorbid alcohol use disorders was inconclusive. Although the majority of data on treatment efficacy in this review were from serotonergic drugs, we rated evidence on this outcome as being of very low quality. This was primarily due to the small number of studies providing data on a clinically diverse population

Cochrane Database of Systematic Reviews | Review - Intervention

Antidepressants for the treatment of people with co-occurring depression and alcohol dependence

Roberta Agabio, Emanuela Trogu, Pier Paolo Pani Authors' declarations of interest

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Abstract

Background

Alcohol dependence is a major public health problem characterized by recidivism, and medical and psychosocial complications. The co-occurrence of major depression in people entering treatment for alcohol dependence is common, and represents a risk factor for morbidity and mortality, which negatively influences treatment outcomes.

Objectives

To assess the benefits and risks of antidepressants for the treatment of people with co-occurring depression and alcohol dependence.

Authors' conclusions

We found low-quality evidence supporting the clinical use of antidepressants in the treatment of people with co-occurring depression and alcohol dependence. Antidepressants had positive effects on certain relevant outcomes related to depression and alcohol use but not on other relevant outcomes. Moreover, most of these positive effects were no longer significant when studies with high risk of bias were excluded. Results were limited by the large number of studies showing high or unclear risk of bias and the low number of studies comparing one antidepressant to another or antidepressants to other medication. In people with co-occurring depression and alcohol dependence, the risk of developing adverse effects appeared to be minimal, especially for the newer classes of antidepressants (such as selective serotonin reuptake inhibitors). According to these results, in people with co-occurring depression and alcohol dependence, antidepressants may be useful for the treatment of depression, alcohol dependence, or both, although the clinical relevance may be modest.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anthenelli 2014	Type of participants not in the inclusion criteria: no depression
Arnow 2015	Type of participants not in the inclusion criteria: no alcohol dependence
Balaratnasingam 2011	Data of single group not available
Bandati 2013	Study design not in the inclusion criteria: no control group
Batki 2015	Type of participants and type of intervention not in the inclusion criteria: no depression, no use of antidepressant medications
Bowman 1966	Type of intervention not in the inclusion criteria: no antidepressant medications used
Brewer 2015	Type of participants and type of intervention not in the inclusion criteria: no depression, no alcohol dependence; no antidepressant medications used
Brown 2003	Study design not in the inclusion criteria: no control group
Brunelin 2014	Type of participants and type of intervention not in the inclusion criteria: no alcohol dependence; no antidepressant medications used
Charney 2015	Type of participants not in the inclusion criteria: only 22% of participants had depression (single data of these participants not available)
Charnoff 1967	Type of participants not in the inclusion criteria: no depression
Chick 2004b	Type of participants not in the inclusion criteria: no depression
Clark 2003	Study population not in the inclusion criteria: people aged < 18 years

What about dopamine antagonists?

META-ANALYSIS

Antipsychotics for Primary Alcohol Dependence: A Systematic Review and Meta-Analysis of Placebo-Controlled Trials

Taro Kishi, MD, PhD; Serge Sevy, MD, MBA; Raja Chekuri, MD, MPH; and Christoph U. Correll, MD

ABSTRACT

Objective: We sought to meta-analytically assess the utility of antipsychotics in patients with primary alcohol dependence.

Data Sources: We searched PubMed, Cochrane Library, and PsycINFO without language restrictions from database inception until December 2012, using the following keywords: (*randomized*, *random*, OR *randomly*) AND (*placebo*) AND (*alcohol dependence*) AND (*neuroleptic* OR *antipsychotic* OR *antidopaminergic* OR the names of 34 individual antipsychotics).

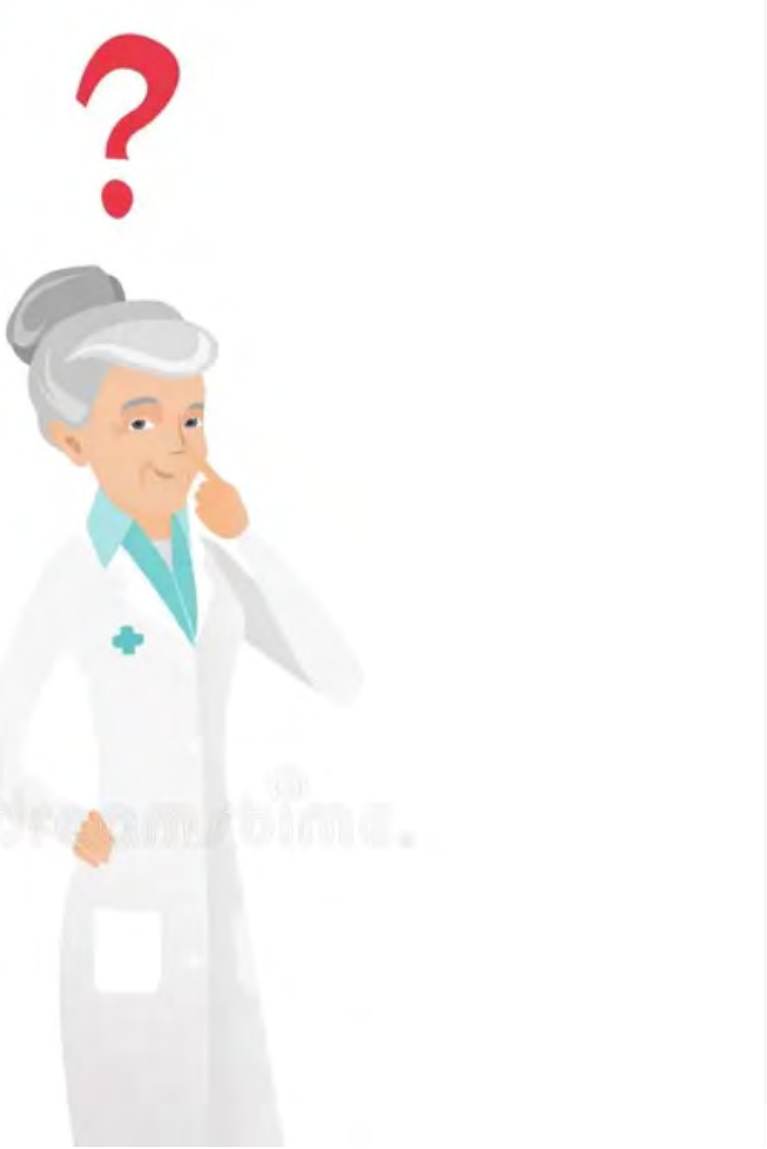
Study Selection: Included in this study were randomized, placebo-controlled trials of antipsychotics lasting ≥ 2 weeks in patients with primary alcohol dependence and without schizophrenia or bipolar disorder.

Data Extraction: Two independent evaluators extracted data. Standardized mean difference (SMD), risk ratio (RR), and numbers needed to harm (NNH) ± 95% confidence intervals (CIs) were calculated.

Results: Across 13 double-blind studies, 1,593 patients were randomly assigned to one of the following: amisulpride (1 study, n = 37), aripiprazole (2 studies, n = 163), flupenthixol decanoate (1 study, n = 142), olanzapine (2 studies, n = 62), quetiapine (4 studies, n = 174), tiapride (3 studies, n = 212), or placebo (13 studies, n = 803). Neither pooled nor individual antipsychotics outperformed placebo regarding relapse prevention (pooled RR = 1.05 [95% CI, 0.95 to 1.16], *P* = .38, 9 studies, n = 1,405).

Alcohol is the most common cause of substance abuse and dependence worldwide.[1,2] Alcohol dependence is a chronic disorder with high risk of relapses, progressive worsening, co-occurring psychiatric and neurologic disorders, and medical complications, such as liver cirrhosis, cardiovascular diseases, and cancer.[1–5] Alcohol dependence is responsible for 4% of global deaths.[3–5] In the United States, excessive alcohol consumption is associated with approximately 75,000 deaths per year and accounts for approximately 40% of all deaths related to traffic accidents.[3–5] Excessive alcohol consumption is also associated with major cost to society due to violence, lost productivity, and health care expenditure. Alcohol dependence contributes to a wide range of social problems, including family disruption and loss of work productivity.[6,7]

The treatment for alcohol dependence includes pharmacotherapy, psychotherapy, and self-help groups such as Alcoholics Anonymous, which are frequently administered in combination. Disulfiram, naltrexone, and acamprosate, but not antipsychotics, have US



A Couple of Problems with this with SSRI and Antipsychotics

1. SSRI and antipsychotics are not effective for treating mental health symptoms in those with AUD.
2. While often unseen elsewhere in medicine, the research supporting routine SSRI use is questioned in EBM circles

Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications


OPEN ACCESS

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Abstract

Objective To determine, using research on duloxetine for major depressive disorder as an example, if there are inconsistencies between protocols, clinical study reports, and main publicly available sources (journal articles and trial registries), and within clinical study reports themselves, with respect to benefits and major harms.

Design Data on primary efficacy analysis and major harms extracted from each data source and compared.

Setting Nine randomised placebo controlled trials of duloxetine (total in journal articles and Lilly trial registry reports, respectively. We also found publication bias in relation to beneficial effects.

Conclusion Clinical study reports contained extensive data on major harms that were unavailable in journal articles and in trial registry reports. There were inconsistencies between protocols and clinical study reports and within clinical study reports. Clinical study reports should be used as the data source for systematic reviews of drugs, but they should first be checked against protocols and within themselves for accuracy and consistency.

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Andrea Cipriani, Toshi A Furukawa, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes*

Summary

Background Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available; however, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, we aimed to update and expand our previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder.

Methods We did a systematic review and network meta-analysis. We searched Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, the websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomised controlled trials from their inception to Jan 8, 2016. We included placebo-controlled and head-to-head trials of 21 antidepressants used for the acute treatment of adults (≥18 years old and of both sexes) with major depressive disorder diagnosed according to standard operationalised criteria. We excluded quasi-randomised trials and trials that were incomplete or included 20% or more of participants with bipolar disorder, psychotic depression, or

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See Comment page 1333

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Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis

Klaus Munkholm, Asger Sand Paludan-Müller, Kim Boesen

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ABSTRACT

Objectives To investigate whether the conclusion of a recent systematic review and network meta-analysis (Cipriani *et al*) that antidepressants are more efficacious than placebo for adult depression was supported by the evidence.

Design Reanalysis of a systematic review, with meta-analyses.

Data sources 522 trials (116 477 participants) as reported in the systematic review by Cipriani *et al* and clinical study reports for 19 of these trials.

Analysis We used the Cochrane Handbook's risk of bias tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the risk of bias and the certainty of evidence, respectively. The impact of several study characteristics and publication status was estimated using pairwise subgroup meta-analyses.

Results Several methodological limitations in the evidence base of antidepressants were either unrecognised or underestimated in the systematic review by Cipriani *et al*. The effect size for antidepressants versus

Strengths and limitations of this study

- ► Empirical evidence was provided showing how many biases and methodological limitations in the evidence base for antidepressants for depression affect the apparent effect size for antidepressants.
- ► For the first time, the impact of the 'placebo run-in' study design on the apparent effect size for antidepressants compared with placebo was estimated.
- ► We reported the effect estimate of antidepressants compared with placebo as a mean difference on the investigator-rated Hamilton depression rating scale to provide an outcome measure that can be easily interpreted by patients and clinicians.
- ► When possible, we compared the data reported by Cipriani *et al* on the outcomes of total dropouts and dropouts due to adverse events with the clinical study reports that we have previously obtained from the European Medicines Agency.
- ► Our analyses relied on the data reported in the systematic review by Cipriani *et al* and we did not

a) differed from the clinical study reports in 12 (63%) of 19 trials. The certainty of the evidence for the placebo-controlled comparisons should be very low according to GRADE due to a high risk of bias, indirectness of the evidence and publication bias. The mean difference between antidepressants and placebo on the 17-item Hamilton depression rating scale (range 0–52 points) was 1.97 points (95% CI 1.74 to 2.21).

Conclusions The evidence does not support definitive conclusions regarding the benefits of antidepressants for depression in adults. It is unclear whether antidepressants are more efficacious than placebo.

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Meta-analyses with industry involvement are massively published and report no caveats for antidepressants

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Abstract

Objectives: To identify the impact of industry involvement in the publication and interpretation of meta-analyses of antidepressant trials in depression.

Study Design and Setting: Using MEDLINE, we identified all meta-analyses evaluating antidepressants for depression published in January 2007–March 2014. We extracted data pertaining to author affiliations, conflicts of interest, and whether the conclusion of the abstract included negative statements on whether the antidepressant(s) were effective or safe.

Results: We identified 185 eligible meta-analyses. Fifty-four meta-analyses (29%) had authors who were employees of the assessed drug manufacturer, and 147 (79%) had some industry link (sponsorship or authors who were industry employees and/or had conflicts of interest). Only 58 meta-analyses (31%) had negative statements in the concluding statement of the abstract. Meta-analyses including an author who were employees of the manufacturer of the assessed drug were 22-fold less likely to have negative statements about the drug than other meta-analyses [1/54 (2%) vs. 57/131 (44%); $P < 0.001$].

Conclusion: There is a massive production of meta-analyses of antidepressants for depression authored by or linked to the industry, and they almost never report any caveats about antidepressants in their abstracts. Our findings add a note of caution for meta-analyses with ties to the manufacturers of the assessed products.

A Couple of Problems with this with SSRI and Antipsychotics

1. SSRI and antipsychotics are not effective for treating mental health symptoms in those with AUD
2. While often unseen elsewhere in medicine, the research supporting routine SSRI use is questioned in EBM circles
3. **SSRI and antipsychotics have an under-appreciated adverse event profile in persons seeking help for AUD***

Review

The role of serotonin in drug use and addiction *

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HIGHLIGHTS

- We review the role of the serotonergic system in the establishment of psychoactive drug use and transition to addiction.
- There is a distinct involvement of the serotonergic system in both processes.
- A new functional model suggests specific serotonergic adaptations during controlled drug use.
- Induced serotonergic adaptations render the nervous system susceptible to the transition to compulsive drug use.
- Serotonergic adaptations often overlap with genetic risk factors for addiction.

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ABSTRACT

The use of psychoactive drugs is a wide spread behaviour in human societies. The systematic use of a drug requires the establishment of different drug use-associated behaviours which need to be learned and controlled. However, controlled drug use may develop into compulsive drug use and addiction, a major psychiatric disorder with severe consequences for the individual and society. Here we review the role of the serotonergic (5-HT) system in the establishment of drug use-associated behaviours on the one hand and the transition and maintenance of addiction on the other hand for the drugs: cocaine, amphetamine, methamphetamine, MDMA (ecstasy), morphine/heroin, cannabis, alcohol, and nicotine. Results show a crucial, but distinct involvement of the 5-HT system in both processes with considerable overlap between psychostimulant and opioidergic drugs and alcohol. A new functional model suggests specific adaptations in the 5-HT system, which coincide with the establishment of controlled drug use-associated behaviours. These serotonergic adaptations render the nervous system susceptible to the transition to compulsive drug use behaviours and often overlap with genetic risk factors for addiction. Altogether we suggest a new trajectory by which serotonergic neuroadaptations induced by first drug exposure pave the way for the establishment of addiction.

Variability in the substance use disorder exclusion criterion in antidepressant efficacy trials

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Affiliations + expand

PMID: 27002283 DOI: 10.1016/j.jad.2016.03.024

Abstract

Background: Substance use disorders are the most commonly excluded psychiatric disorder in antidepressant efficacy trials (AETs). In a recent review of AETs we noticed variability in the definition of the substance use disorder exclusion criterion. In the present report we examined in greater detail the variability in defining the substance use disorder exclusion criterion, the potential impact of this variability on excluding patients from an AET, and whether the definition of the criterion has changed in the past 20 years.

Methods: We identified 170 AETs published during the past 20 years and compared the studies published during the past 5 years (n=56) to the studies published during the 15 prior years (n=114).

Results: Substance abuse was more frequently used as an exclusion criterion than substance dependence. Six time frames have been used as the basis of exclusion, the most frequent being the past 12 months. The time frame had a greater impact on the number of patients who would be excluded than the abuse/dependence distinction. The definition of the substance use exclusion criterion was no different in the studies of the past 5 years compared to the prior 15 years.

Limitations: A limitation of the present analysis is that it was based on published placebo-controlled studies of antidepressants.

Conclusion: Studies varied in whether abuse or dependence was the basis of exclusion, whether alcohol or illicit drugs or both were the basis of exclusion, and the time frame of the disorders' presence. We raise the question of whether the routine exclusion of patients with a substance use disorder should be reflected in a product's label.

Increased alcohol consumption in rats after subchronic antidepressant treatment

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Abstract

The use of antidepressants for alcoholism in humans has been a matter of controversy in recent years. Despite the existence of an important co-morbidity for depression and alcoholism, some studies suggest that the use of antidepressants could worsen the prognosis of alcoholism. However, there is a lack of studies in animal models exploring this phenomenon. In the present study, we show how the 15-d treatment with fluoxetine (10 mg/kg) or venlafaxine (50 mg/kg) affected alcohol deprivation effect (ADE) and subsequent alcohol consumption. Initially, fluoxetine reduced ADE and venlafaxine did not affect it. However, in the following days, both antidepressants increased alcohol consumption, an effect that was found to last at least 5 wk. Fluoxetine treatment was shown to cause a locomotor sensitized response to

New onset alcohol dependence linked to treatment with selective serotonin reuptake inhibitors

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Abstract.
BACKGROUND: Genetic and environmental factors influence the development of alcohol dependence and alcohol dependence increases the risk of developing Major Depressive Disorder-MDD (vice versa). Amongst antidepressants, the selective serotonin reuptake inhibitors (SSRIs) are likely the most frequently prescribed for MDD. However, findings on the role of SSRIs in alleviating alcoholism are conflicting.
CASE DESCRIPTION: A review of the literature is highlighted with a case of middle-aged lady with new onset alcohol dependence syndrome after commencement of SSRI, which resolved following discontinuation of the SSRIs and the introduction of Mirtazapine.
DISCUSSION: The serotonin transporter gene has been linked to excessive drinking, early-onset problem drinking, alcohol dependence, anxiety and impulsiveness. While the evidence for antidepressant use appears consistent in alleviating depressive symptoms in patients with comorbid alcohol dependence and depression, some groups of patients may show an increase in alcohol consumption. Alternatively, there are a series of studies suggesting that antagonism of S-3 receptors can lead to diminished cravings for alcohol. This case highlights the need for further research into the effects of SSRIs on alcohol consumption in those with and without previous alcohol dependence syndromes. It also indicates a need to monitor changes in alcohol consumption and behaviour while on SSRIs.

IOS Press

Ninety-three cases of alcohol dependence following SSRI treatment

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Abstract.
BACKGROUND: There have been recent reports linking serotonin reuptake inhibitor use with increased alcohol consumption. A syndrome of alcoholism precipitated by a common treatment has clear implications for both research and treatment if it is a common phenomenon.
OBJECTIVE: To explore the profile of people affected, and drugs that might trigger the syndrome.
METHODS: We have selected reports to RxISK.org reporting the problem and cases linked to a blog posting outlining the syndrome and mined these for data on age, gender, drug of use, pattern of outcome on treatment, and impact of the problem.
RESULTS: The data make it clear that all treatments with significant effects on the serotonin reuptake system are likely to cause this problem. Both sexes, and all ages are affected and reports have come from a range of countries. While stopping treatment can lead to the problem clearing, a failure to stop can result in death.
CONCLUSIONS: SSRI induced alcoholism is likely to be a relatively common problem. Recognizing the problem can lead to a gratifying cure. A failure to recognize it can be fatal.

Severe alcohol use disorder after initiation of selective serotonin reuptake inhibitor therapy

Preet Gandhi MSc, David Healy MD, Nikki Bozinoff MD MSc

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See related article at www.cmaj.ca/lookup/doi/10.1503/cmaj.230715.

A 52-year-old woman was admitted to a facility for assistance with alcohol withdrawal. She described symptoms of severe cravings, involving a 6-month period of escalating alcohol use. She received a diagnosis of severe alcohol use disorder (AUD) meeting all 11 *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for AUD. Her alcohol use had increased from approximately a half bottle of wine daily (about 2.6 Canadian standard drinks[1]) in the evening at baseline, to morning alcohol use and a total of approximately 2 bottles of wine, plus additional spirits (about 18 standard drinks) daily.

She reported that before the emergence of severe AUD, she was employed, married and stably housed. She stated that her long-standing baseline use was associated with working in an industry where socializing with alcohol was common. However,

Key points

- Antidepressants of the selective serotonin reuptake inhibitor (SSRI) class are commonly prescribed in Canada, including to people with, and at risk of, alcohol use disorders (AUDs).
- Meta-analyses suggest that depressive symptoms may not improve with SSRI therapy in people with concurrent AUD.
- Clinicians should offer treatment of underlying AUD with first-line pharmacologic (e.g., naltrexone) and behavioural interventions.
- Clinicians should also be aware that some patients may develop AUD or have their AUD aggravated by SSRIs.

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Editorial

OXFORD

Editorial

Unhelpful Prescribing in Alcohol Use Disorder: Risk and Averting Risk

At Scottish medical schools we were taught that to over-prescribe was the 8th venial sin. We learnt about the terrors of interactions at the level of absorption, metabolism, excretion and the curse of multiplying unwanted effects.

I intercede before Asclepius for my colleagues in psychiatry and primary care who have difficulty identifying alcohol problems in their patients (see Mitchell *et al.*, 2012) or who have difficulty understanding that alcohol use disorders (AUD) are often the cause not the consequence of their patients' complaints of depression and anxiety.

In 2014–2015, 222 consecutive new admissions to a short stay addictions clinic in New Zealand were asked about the medicines they were already prescribed. Their primary substance use disorder was mainly alcohol (64.4%) but some were mainly users of cannabis (9.9%), synthetic cannabinoid (9.0%), opioids (5.9%) or stimulants (9.9%). It emerged that 58.6% were already taking antidepressants, 47.7% antipsychotics (mainly quetiapine—range 12.5–800 mg, median 50 mg for 'agitation, anxiety or sleep'), 2.3% a benzodiazepine and 2.7% an anticonvulsant. Overall, 79.3% were prescribed at

ANTIDEPRESSANTS

It is well known that excessive drinking is associated with depression.

When Iovieno *et al.* (2011) examined the evidence for the effect of antidepressants on depression in depressed patients with AUD, only tricyclics (seldom used today) and nefazodone (now discontinued) had an effect. There have been further studies with SSRIs, which have shown little effect, although when naltrexone is prescribed as well, a trend towards improved mood emerges (Pettinati *et al.*, 2010).

Overall, the benefits to depressive symptoms in these studies are equivocal. The Cochrane Review (Agabio *et al.*, 2018) of 33 studies covering 2242 patients found that most of the effects were no longer significant when studies with high risk of bias were excluded. This reflected the earlier meta-analysis of Torrens *et al.* (2005) who found no evidence that antidepressants reduced drinking. However, Foulds *et al.* (2015) in a meta-analysis that included only 11 studies were

frontiers in Psychiatry

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Treatment of Comorbid Alcohol Dependence and Anxiety Disorder: Review of the Scientific Evidence and Recommendations for Treatment

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Patients with alcohol-use disorders (AUDs) have a high prevalence of anxiety disorders (AnxDs). "Co-occurring disorders" refers to the coexistence of an AUD and/or drug related disorders with another non-addictive psychiatric disorder. The aim of this study was to assess the effectiveness of psychopharmacological treatments and psychotherapy in patients with AUD and AnxD and to propose recommendations for the treatment of patients with comorbid AnxDs and AUDs. Randomized clinical trials, meta-analyses, and clinical guidelines were retrieved from PubMed, Embase, and Cochrane databases. Paroxetine was found to be effective in social anxiety patients with alcohol dependence. Selective serotonin reuptake inhibitors (SSRIs), especially sertraline, showed effective results in posttraumatic stress disorder and in comorbid AnxD–AUD. However, SSRIs should be used with caution when patients are actively drinking because they may increase alcohol consumption. Buspirone, gabapentin, and pregabalin were found to be effective in comorbid AnxD–AUD. The treatment of dual AnxDs should start as early as possible. Since AUDs and AnxDs can reinforce each other, treatments targeting both

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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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A Placebo-Controlled, Double-Blind Study of Fluoxetine in Severe Alcohol Dependence: Adjunctive Pharmacotherapy During and After Inpatient Treatment

David I. Kabel and Frederick Petty

Twenty-eight male patients with severe alcohol dependence (mean pretreatment consumption of 18.6 standard drinks per day) completed a placebo-controlled, double-blind clinical trial of fluoxetine (60 mg/day). They were assigned to medication group in the second of 4 weeks on a voluntary inpatient chemical dependency ward and continued medication during a 12-week follow-up phase. Fluoxetine did not reduce clinically significant relapse rates: only 8 of 15 (53%) of fluoxetine subjects remained sober at 12 weeks, compared with 9 of 13 (69%) of the placebo group (Fisher's exact test, $p = 0.46$). Subjects with comorbid cocaine dependence relapsed more than twice as often (3 of 4, 75%) as those with alcohol dependence alone (8 of 24, 33%), although this trend did not reach statistical significance because of the small number of dually dependent subjects (Mann Whitney U test = 68, $p = 0.13$). Supportive living arrangements after hospital discharge did reduce relapse rates: 8 of 9 subjects (89%) discharged to a Veterans Affairs domiciliary were sober at 12 weeks, compared with 9 of 19 (47%) subjects discharged back to the community (Mann-Whitney U test = 125, $p = 0.02$). Fluoxetine-treated subjects who remained sober at 12 weeks reported a significant decrease in mean subjective alcohol craving scores from 2.9 to 0.7 on a 10-point scale ($t = 2.828$, $p = 0.02$). In summary, fluoxetine did not reduce clinical relapse rates in this sample of male severe alcoholics without other axis I disorders who completed 4 weeks of inpatient alcoholism treatment.

Key Words: Alcoholism, Fluoxetine, Selective Serotonin Reuptake Inhibitors.

lopram, the 5-HT_{1A} agonist buspirone, the 5-HT_3 antagonist ondansetron, and the 5-HT_{1C}/5-HT_2 antagonist ritanserin.[3–6]

Serotonergic agents such as SSRI can also reduce alcohol consumption in humans. Three SSRI not available commercially in the United States (zimelidine, citalopram, and viqualine) have been shown to reduce alcohol intake significantly in nondepressed, outpatient alcohol abusers.[7–10] Ritanserin and ondansetron in small trials have also shown the ability to decrease alcohol intake in alcoholics.[11,12] Naranjo et al.[13] reported that fluoxetine (60 mg/day) produced a significant 17% decrease from baseline total and mean daily alcoholic drinks in outpatient alcohol abusers.

Gorelick and Paredes[14] treated alcohol-dependent inpatients with fluoxetine (up to 80 mg/day) in a fixed-interval drinking decision procedure. The fluoxetine group had a significant but transient 14% decrease in mean daily alcohol consumption and an associated decrease in alcohol craving in the first of four treatment weeks only. Fluoxetine-treated subjects returned an unfinished drink significantly more often than controls, suggesting that SSRI may produce a taste aversion to alcohol in humans, as they do in

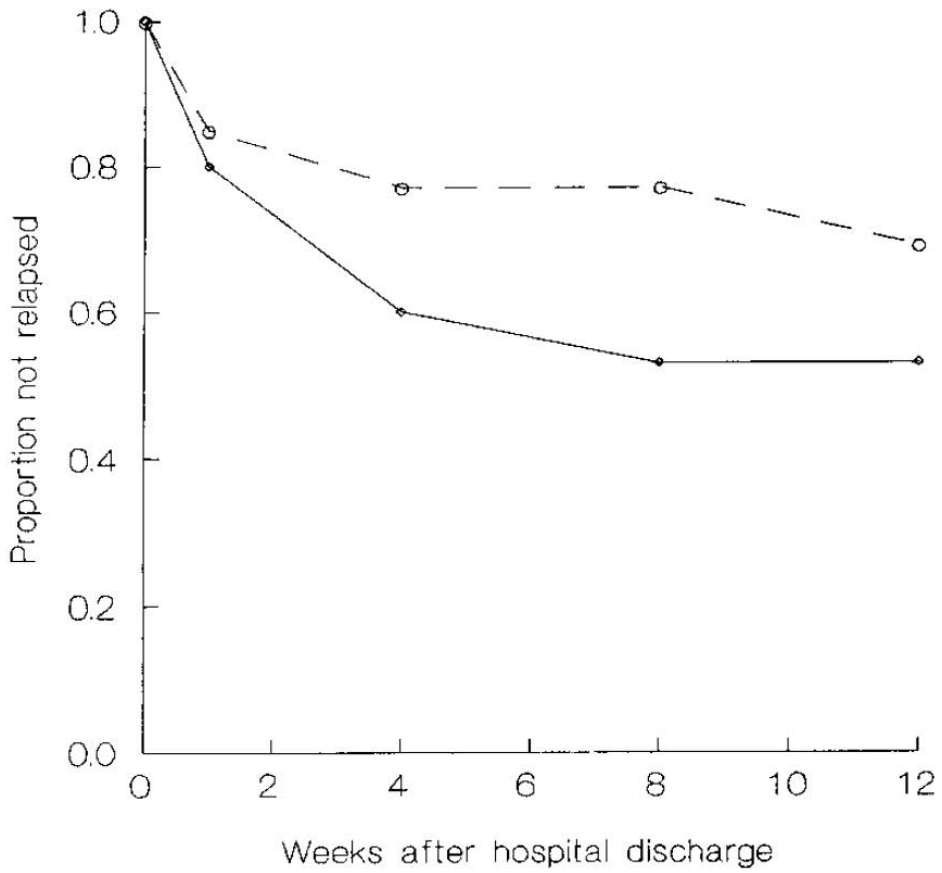

Fig. 1. Proportion of subjects sober (not clinically relapsed) over follow-up phase, by drug group. ○ - - - ○, Placebo (n = 13); ●——●, drug (n = 15).

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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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Fluoxetine Treatment Seems to Reduce the Beneficial Effects of Cognitive-Behavioral Therapy in Type B Alcoholics

Henry R. Kranzler, Joseph A. Burleson, Joseph Brown, and Thomas F. Babor

Objective: **The aim of this study was to test the hypothesis that, because of abnormalities in serotonergic neurotransmission that may underlie craving and impulsive be differentially affects drinking among typ acterized by high levels of both premor related problems. *Methods:* Using a *k*- alcohol-dependent subjects from a pla etine were grouped into low-risk/sever risk/severity (type B: *n* = 35) groups. M ance (with pretreatment measures a effects of Alcoholic Subtype, Medicatio tion, and their interactions on measure 12-week treatment period and a 6-mon Although there were no main effects o cation Group, subjects who completed significantly better drinking-related ou interaction of Alcoholic Subtype by Me ment. Among type B subjects, fluox

and natural history, an implicit assumption of typological

ceived placebo. Those investigators concluded that the effectiveness of counseling was diminished when combined with fluoxetine treatment. A medication-mediated reduction in the beneficial effects of relapse prevention training, such as appears to be the case both in the study by Covi et al.[55] and in the present study, has important clinical implications that are underscored by the widespread use of fluoxetine.

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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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Sertraline Treatment for Alcohol Dependence: Interactive Effects of Medication and Alcoholic Subtype

Helen M. Pettinati, Joseph R. Volpicelli, Henry R. Kranzler, Gary Luck, Margaret R. Rukstalis, and Avital Cnaan

Background: Characteristic behaviors of some alcohol-dependent individuals, e.g., binge drinking, comorbid psychopathology, and some types of alcohol-related problems, have been linked to abnormalities in serotonergic neurotransmission. However, studies that have evaluated serotonergic pharmacotherapy for reducing drinking have yielded conflicting results. One explanation for these findings is a general failure to distinguish alcohol subgroups that may be differentiated on the basis of serotonergic abnormalities. However, in 1996, Kranzler and colleagues reported that Type B alcoholics, who are characterized by high levels of premorbid vulnerability, alcohol dependence severity, and comorbid psychopathology, showed less favorable drinking outcomes in response to treatment with fluoxetine, a serotonin reuptake inhibitor, than with placebo. This medication effect was not seen in Type A alcoholics, i.e., those with lower risk/severity of alcoholism and psychopathology. The aim of the present study was to explore the validity of differential responding by alcohol-dependent subtypes using the serotonin reuptake inhibitor, sertraline.

Methods: A *k*-means clustering procedure was applied to a sample of alcohol-dependent subjects enrolled in a 14-week, placebo-controlled trial of 200 mg/day of sertraline, classifying them into lower-risk/severity (Type A: $n = 55$) and higher-risk/severity (Type B: $n = 45$) subgroups.

Results: A significant interaction between alcoholic subtype and medication condition was found, confirming the findings of Kranzler and colleagues that alcoholic subtypes responded differentially to serotonergic medication. Somewhat at variance with their results, however, the present study showed that the lower risk/severity (Type A) subjects had more favorable outcomes when treated with sertraline compared to placebo.

Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double-blind, placebo-controlled multicentre study with analysis by typology

Jonathan Chick [a,*], Harald Aschauer [b], Kurt Hornik [c], on behalf of the Investigators' Group [1]

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Abstract

Patients with a diagnosis of alcohol dependence, detoxified and abstinent for 10–30 days, were randomly allocated to placebo or the serotonin reuptake inhibitor, fluvoxamine (up to 300 mg per day), plus counselling and support.

In the intention to treat sample of 493, there was a trend for the fluvoxamine group to do worse than the placebo group on the primary outcome criteria: abstinence; and relapse defined as drinking ≥5 units on an occasion and ≥4 such occasions in a week, or ≥12 units on an occasion (1 unit = 9 g ethanol).

When typology of alcoholism was assigned by scores on the Tridimensional Personality Questionnaire, Types I and II had similar rates of survival without relapse on placebo (PLC I: 19.3%, $n = 135$; PLC II: 18.2%, $n = 110$), but on fluvoxamine Type II did worse than Type I (FLU I: 13.7%, $n = 131$; FLU II: 6.14%, $n = 114$) ($P < 0.01$). When typology was assigned on the basis of age of onset of alcohol problems (≤ or > age 25), early-onset patients in the fluvoxamine group relapsed more frequently than late-onset patients in that group (no longer significant after adjustment for gender), as did those who commenced regular drinking before age 25 (both with and without adjustment for gender). One explanation for our finding could be that impulsivity in early-onset or Type II patients may be accentuated by serotonin enhancement.

A Double-Blind, Randomized Trial of Sertraline for Alcohol Dependence

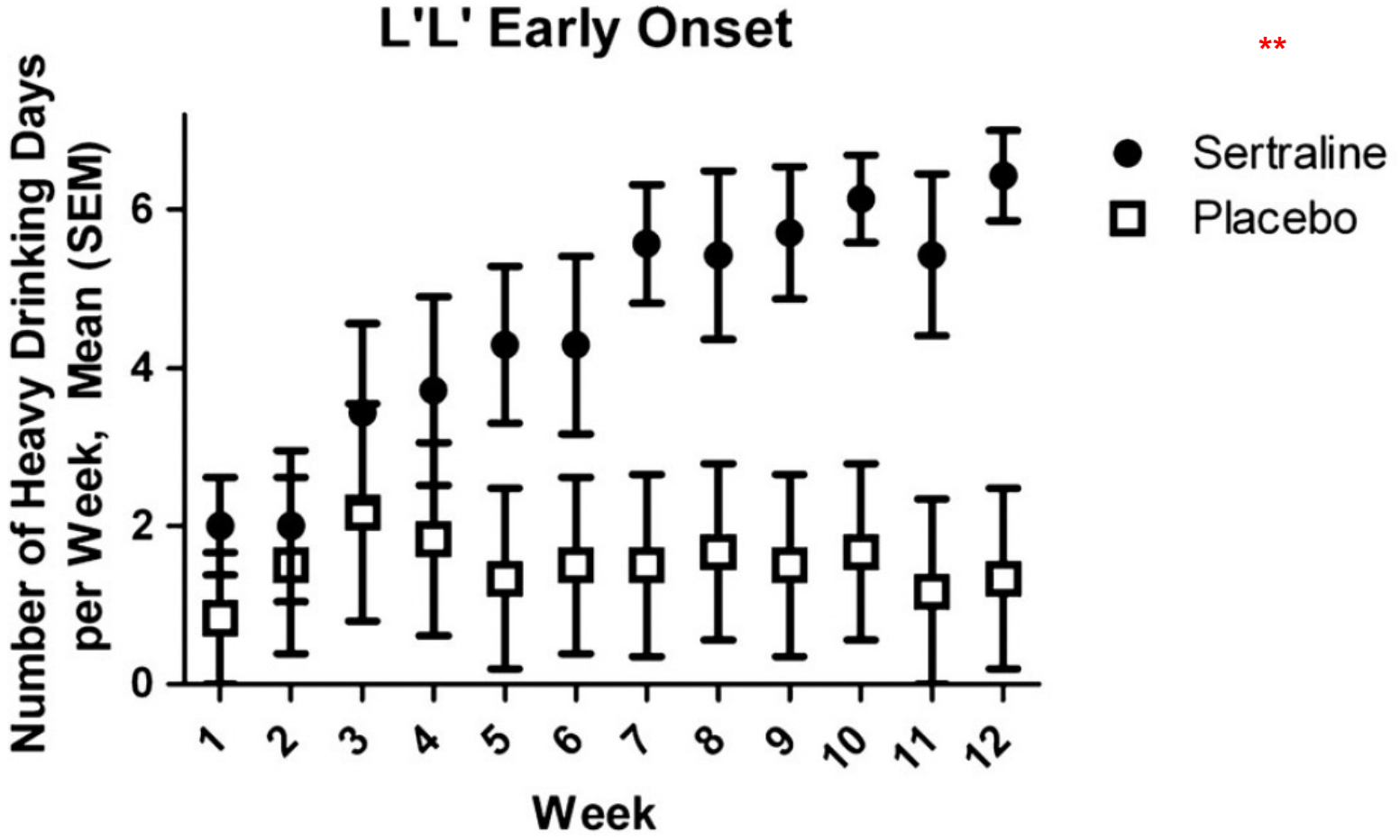
Moderation by Age of Onset and 5-Hydroxytryptamine Transporter-Linked Promoter Region Genotype

Henry R. Kranzler, MD,† Stephen Armeli, PhD,‡ Howard Tennen, PhD,§ Jonathan Covault, MD, PhD,* Richard Feinn, PhD,* Albert J. Arias, MD,* Helen Pettinati, PhD,|| and Cheryl Oncken, MD¶*

Abstract: Late-onset/low-vulnerability alcoholics (LOAs) appear to drink less when treated with a selective serotonin reuptake inhibitor than placebo, whereas early-onset/high-vulnerability alcoholics (EOAs) show the opposite effect. We conducted a 12-week, parallel-group, placebo-controlled trial of the efficacy of sertraline in alcohol dependence (AD). We compared the effects in LOAs versus EOAs and examined the moderating effects of a functional polymorphism in the serotonin transporter gene. Patients (N = 134, 80.6% male, 34.3% EOAs) with *Diagnostic and Statistical Manual of Mental Disorders-IV* AD received up to 200 mg of sertraline (n = 63) or placebo (n = 71) daily. We used

(*J Clin Psychopharmacol* 2011;31: 22–30)

Although increasing serotonin (5-hydroxytryptamine [5-HT]) consistently reduces drinking in preclinical models,[1] serotonergic agonists have yielded limited and inconsistent effects on drinking in humans.[2–5] Efforts to subtype alcoholics may help reduce this inconsistency. For example, in patients with an earlier onset of alcoholism and high levels of both premorbid and alcohol-related problems (i.e., type B alcoholics[6]), fluoxetine


L'L' Early Onset
**
Number of Heavy Drinking Days per Week, Mean (SEM)
0
2
4
6
1
2
3
4
5
6
7
8
9
10
11
12
Week
Sertraline
Placebo

approximately 25%. The current U.S. prevalence of AD was estimated to be 3.8%[51] (ie, 2.4% EOAs and 1.3% LOAs [B. Grant, personal communication, February 3, 2010]). If one fourth of those individuals are responsive to SSRI treatment, as much as 0.6% of the total U.S. population could be adversely affected and more than 0.3% could benefit from the medication.

for mood or anxiety disorders.[53] The high prevalence of AD and the widespread use of antidepressants suggest that the findings reported here are relevant to a substantial proportion of the U.S. population.

Poorer Drinking Outcomes with Citalopram Treatment for Alcohol Dependence: A Randomized, Double-Blind, Placebo-Controlled Trial

Dara A. Chamey, Laura M. Heath, Eugenia Zikos, Jorge Palacios-Boix, and Kathryn J. Gill

Background: Previous research on the use of selective serotonin reuptake inhibitors (SSRIs) as a treatment for alcohol dependence has yielded mixed results. Depression has been shown to be a predictor of relapse and poor outcome following treatment, and it has been hypothesized that SSRIs would be beneficial in reducing drinking in depressed alcohol-dependent individuals. This randomized, double-blind, placebo-controlled trial was designed to test the effects of citalopram on treatment outcomes among alcohol-dependent individuals with and without depression.

Methods: Two hundred and sixty-five patients meeting criteria for a DSM-IV diagnosis of alcohol abuse or dependence were randomly assigned to receive placebo or citalopram 20 mg per day for the first week, followed by 40 mg per day from weeks 2 through 12. All patients received a standard course of treatment consisting of weekly individual and group psychotherapy. Participants were reassessed at 12 weeks, including dropouts from both treatment groups to determine rates of abstinence, changes in alcohol use, addiction severity, depressive symptoms, and psychiatric status.

Results: Citalopram provided no advantage over placebo in terms of treatment outcomes, and for some measures, citalopram produced poorer outcomes. Patients in the citalopram group had a higher number of heavy drinking days throughout the trial, and smaller changes in frequency and amount of alcohol consumption at 12 weeks. There was no influence of depression severity on outcomes in either medication group. Survival analyses also indicated no differences between depressed and nondepressed patients in the citalopram group for time to first slip or relapse. A diagnosis of personality disorder was associated with poorer treatment responses overall, regardless of treatment condition.

Conclusions: This trial does not support the use of citalopram in the treatment of alcohol dependence. The results suggest that the use of SSRIs among depressed and nondepressed alcohol-dependent individuals early in recovery, prior to the onset of abstinence, may be contraindicated.

What about Trazodone?

Alcoholism: Clinical and Experimental Research

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Trazodone for Sleep Disturbance After Alcohol Detoxification: A Double-Blind, Placebo-Controlled Trial

Peter D. Friedmann, Jennifer S. Rose, Robert Swift, Robert L. Stout, Richard P. Millman, and Michael D. Stein

Background: Trazodone is a commonly prescribed off-label for sleep disturbance in alcohol-dependent patients, but its safety and efficacy for this indication is unknown.

Methods: We conducted a randomized, double-blind, placebo-control trial of low-dose trazodone (50 to 150 mg at bedtime) for 12 weeks among 173 alcohol detoxification patients who reported current sleep disturbance on a validated measure of sleep quality or during prior periods of abstinence. Primary outcomes were the proportion of days abstinent and drinks per drinking day over 6-months; sleep quality was also assessed.

Results: Urn randomization balanced baseline features among the 88 subjects who received trazodone and 85 who received placebo. The trazodone group experienced less improvement in the proportion of days abstinent during administration of study medication (mean change between baseline and 3 months: −0.12; 95% CI: −0.15 to −0.09), and an increase in the number of drinks per drinking day on cessation of the study medication (mean change between baseline and 6 months, 4.6; 95% CI: 2.1 to 7.1). Trazodone was associated with improved sleep quality during its administration (mean change on the Pittsburgh Sleep Quality Index between baseline and 3 months: −3.02; 95% CI: −3.38 to −2.67), but after it was stopped sleep quality equalized with placebo.

Conclusions: Trazodone, despite a short-term benefit on sleep quality, might impede improvements in alcohol consumption in the postdetoxification period and lead to increased drinking when stopped. Until further studies have established benefits and safety, routine initiation of trazodone for sleep disturbance cannot be recommended with confidence during the period after detoxification from alcoholism.

Key Words: Alcohol-Related Disorders, Sleep Disturbance, Insomnia, Trazodone.

Advocacy for Trazodone?

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DRUG METABOLISM AND DISPOSITION

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METABOLISM & DISPOSITION

TRAZODONE IS METABOLIZED TO *m*-CHLOROPHENYLPIPERAZINE BY CYP3A4 FROM HUMAN SOURCES

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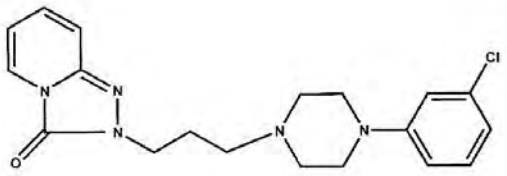
This paper is available online at http://www.dmd.org

ABSTRACT:

The metabolism of the antidepressant drug trazodone to its active metabolite, *m*-chlorophenylpiperazine (mCPP), was studied *in vitro* using human liver microsomal preparations and cDNA-expressed human cytochrome P450 (P450) enzymes. The kinetics of mCPP formation from trazodone were determined, and three *in vitro* experiments were performed to identify the major P450 enzyme involved. Trazodone (100 μM) was incubated with 16 different human liver microsomal preparations characterized for activities of 7 different P450 isoforms. The production of mCPP correlated significantly with activity of cytochrome P4503A4 (CYP3A4) only. Trazodone (100 μM) was then incubated with microsomes from cells expressing human CYP1A1, CYP1A2, CYP2C8, CYP2C9arg, CYP2C9cys, CYP2C19, CYP2D6, or CYP3A4. Only incubations with CYP3A4 resulted in mCPP formation. In the third experiment, the CYP3A4 inhibitor ketoconazole was found to inhibit mCPP formation concentration dependently in both human liver microsomes and in microsomes from cells expressing human CYP3A4. The present results indicate that trazodone is a substrate for CYP3A4, that CYP3A4 is a major isoform involved in the production of mCPP from trazodone, and that there is the possibility of drug-drug interactions with trazodone and other substrates, inducers and/or inhibitors of CYP3A4.

Adverse pharmacokinetic drug interactions may occur when drugs that are substrates, inducers and/or inhibitors of the same cytochrome P450 (P450)[2] enzymes are co-administered, potentially altering the expected rate of metabolism of one or both compounds. The clinical consequences can range from a lack of therapeutic efficacy to severe toxicity and, in extreme cases, fatality. Therefore, it is important to identify the major enzymes involved in the metabolism of a drug so that such interactions can be predicted and avoided.

Trazodone is a triazolopyridine antidepressant drug (fig. 1), which is thought to act through combined 5-HT_2 antagonism and 5-HT reuptake blockade (Haria *et al.*, 1994). It is often co-prescribed with other antidepressants as a sleep-inducing agent because of its sedative side effects (Fabre, 1990; Jacobsen, 1990, Nierenberg *et al.*, 1994) or as an augmentation strategy (Maes *et al.*, 1997). This co-prescription



TRAZODONE

Pharmacologically induced alcohol craving in treatment seeking alcoholics correlates with alcoholism severity, but is insensitive to acamprosate

John C Umhau[1], Melanie L Schwandt[1], Julie Usala[1], Christopher Geyer[1], Erick Singley[1], David T George[1] and Markus Heilig*[,1]

[1]*Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, USA*

Modulation of alcohol craving induced by challenge stimuli may predict the efficacy of new pharmacotherapies for alcoholism. We evaluated two pharmacological challenges, the α_2-adrenergic antagonist yohimbine, which reinstates alcohol seeking in rats, and the serotonergic compound meta-chlorophenylpiperazine (mCPP), previously reported to increase alcohol craving in alcoholics. To assess the predictive validity of this approach, the approved alcoholism medication acamprosate was evaluated for its ability to modulate challenge-induced cravings. A total of 35 treatment seeking alcohol dependent inpatients in early abstinence were randomized to placebo or acamprosate (2997 mg daily). Following two weeks of medication, subjects underwent three challenge sessions with yohimbine, mCPP or saline infusion under double blind conditions, carried out in counterbalanced order, and separated by at least 5 days. Ratings of cravings and anxiety, as well as biochemical measures were obtained. In all, 25 subjects completed all three sessions and were included in the analysis. Cravings were modestly, but significantly higher following both yohimbine and mCPP challenge compared with saline infusion. The mCPP, but not yohimbine significantly increased anxiety ratings. Both challenges produced robust ACTH, cortisol and prolactin responses. There was a significant correlation between craving and the degree of alcoholism severity. Acamprosate administration did not influence craving. Both yohimbine and mCPP challenges lead to elevated alcohol craving in a clinical population of alcoholics, and these cravings correlate with alcoholism severity. Under the experimental conditions used, alcohol cravings induced by these two stimuli are not sensitive to acamprosate at clinically used doses.

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Keywords: alcoholism; craving; yohimbine; meta-chlorophenylpiperazine; acamprosate

Clinical Trial > Nervenarzt. 2005 Mar;76(3):295-307. doi: 10.1007/s00115-004-1763-y.

[Combination treatment with SSRI and cognitive behavior therapy for relapse prevention of alcohol-dependent men. Results of a randomized, controlled multicenter therapeutic study]

[Article in German]

M Hautzinger [1], H Wetzel, A Szegedi, A Scheurich, B Lörch, P Singer, D Schläfke, H Sittinger, T Wobrock, M J Müller, I Anghelescu

“Nefazodone is a analogue of trazodone of which m-CPP is a psychoactive metabolite”

Abstract

Background: This study evaluates the serotonergic antidepressant nefazodone (SSRI) vs placebo (PL) and specific cognitive-behavioral therapy (CBT) vs nondirective group counseling (GC) for relapse prevention in alcohol dependence in a large, prospective, randomized and placebo-controlled, double-blind study at three German university centers.

Methods: Male patients fulfilling at least five criteria for alcohol dependence according to DSM-IV and ICD-10 were eligible, after detoxification, for one of the following treatment combinations: SSRI+CBT, SSRI+GC, PL+CBT, and PL+GC. The SSRI or PL were administered throughout the evaluation period of 15 months. CBT or GC was applied during the first 12 weeks as group therapy according to operationalized manuals. The main outcome measures (assessed at 3 and 12 months of treatment) were the cumulative number of abstinent days, the amount of ethanol consumed during specified evaluation periods of 3 and 12 months, the number of relapses, and the duration of time until first relapse.

Results: After 12 weeks of treatment, no statistically significant differences in any outcome measure were observed between the four treatment combinations. After 52 weeks, the only significant difference was observed in the amount of ethanol consumed, with the SSRI+GC group showing higher intake.

Conclusions: The results of this carefully designed clinical trial suggest that the four treatment combinations do not differ substantially in their efficacy in relapse prevention of nondepressed, severely alcohol-dependent patients. Nefazodone may even promote ethanol drinking in a subset of patients. Cognitive-behavioral therapy as performed in this study was associated with little additional benefit compared with structured GC.

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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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Treatment Outcomes in Type A and B Alcohol Dependence 6 Months After Serotonergic Pharmacotherapy

William Dundon, Kevin G. Lynch, Helen M. Pettinati, and Craig Lipkin

Background: Evidence supporting the use of serotonergic medications for the treatment of alcohol dependence is available from studies where pharmacotherapy targeted specific alcoholic subtypes. We previously established with Babor's alcohol typology that type A "lower risk/severity" alcoholics ($n = 55$) had better treatment response to 14 weeks of sertraline (200 mg/day) than placebo, and this was not found for type B "higher risk/severity" alcoholics ($n = 45$). The purpose of this study was to assess in this original study group whether treatment gains in the type A alcoholics were maintained or whether treatment outcomes changed for the type B alcoholics after discontinuing pharmacotherapy.

therapy. We found that type B alcoholics who had been treated with sertraline, in contrast to placebo, continued to show no advantage for pharmacotherapy in the 6 months after completing treatment. In addition, heavy drinking in type B alcoholics increased over the 6 months postpharmacotherapy in those initially treated with sertraline compared with placebo.

The effects of venlafaxine and cognitive behavioral therapy alone and combined in the treatment of co-morbid alcohol use-anxiety disorders

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ABSTRACT

The effects of the antidepressant venlafaxine (VEN-225 mg daily) and transdiagnostic cognitive behavioral treatment (CBT) alone and in combination on alcohol intake in subjects with co-morbid alcohol use disorders (AUDs) and anxiety disorders were compared. Drinking outcomes and anxiety were assessed for 81 subjects treated for 11 weeks with one of 4 conditions: 1) VEN–CBT, 2) VEN-Progressive Muscle Relaxation therapy (PMR), 3) Placebo (PLC)-CBT and 4) a comparison group of PLC-PMR. For subjects who reported taking at least one dose of study medication, the Time × Group interaction was significant for percent days of heavy drinking and drinks consumed per day. For the measure of percent days heavy drinking, the paired comparison of PLC-CBT versus PLC-PMR group indicated that the PLC-CBT group had greater drinking reductions, whereas other groups were not superior to the comparison group. In Week 11, the proportion of subjects in the PLC-CBT group that had a 50% reduction from baseline in percent days heavy drinking was significantly greater than those in the comparison group. Of the 3 "active treatment" groups only the PLC-CBT group had significantly decreased heavy drinking when contrasted to the comparison group. This finding suggests that the transdiagnostic CBT approach of Barlow and colleagues may have value in the management of heavy drinking in individuals with co-morbid alcoholism and anxiety.

What about polysubstance users?*

ELSEVIER

Journal of Substance Abuse Treatment 40 (2011) 255–264

Journal of Substance Abuse Treatment

Regular article

A randomized controlled trial of fluoxetine in the treatment of cocaine dependence among methadone-maintained patients

Erin L. Winstanley, (Ph.D.)[a,b,*], George E. Bigelow, (Ph.D.)[c], Kenneth Silverman, (Ph.D.)[c], Rolley E. Johnson, (M.D.)[c,d], Eric C. Strain, (M.D.)[c]

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Received 30 June 2010; received in revised form 11 November 2010; accepted 22 November 2010

Abstract

Background: Cocaine abuse and dependence continue to be widespread. Currently, there are no pharmacotherapies shown to be effective in the treatment of cocaine dependence. **Methods:** A 33-week outpatient clinical trial of fluoxetine (60 mg/day, po) for cocaine dependence that incorporated abstinence-contingent voucher incentives was conducted. Participants (N = 145) were both cocaine and opioid dependent and treated with methadone. A stratified randomization procedure assigned subjects to one of four conditions: fluoxetine plus voucher incentives (FV), placebo plus voucher incentives (PV), fluoxetine without vouchers (F), and placebo without vouchers (P). Dosing of fluoxetine/placebo was double blind. Primary outcomes were treatment retention and cocaine use based on thrice-weekly urine testing. **Results:** The PV group had the longest treatment retention (M = 165 days) and lowest probability of cocaine use. The adjusted predicted probabilities of cocaine use were 65% in the P group, 60% in the F group, 56% in the FV group, and 31% in the PV group. **Conclusions:** Fluoxetine was not efficacious in reducing cocaine use in patients dually dependent on cocaine and opioids.

Keywords: Cocaine; Contingency management; Fluoxetine; Methadone

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Journal of Substance Abuse Treatment 40 (2011) 255–264

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Regular article

A randomized controlled trial of fluoxetine in the treatment of cocaine dependence among methadone-maintained patients

Erin L. Winstanley, (Ph.D.)[a,b,*], George E. Bigelow, (Ph.D.)[c], Kenneth Silverman, (Ph.D.)[c],

.00) when all study weeks were included. In a subanalysis of subjects with persistent clinically meaningful depressive symptoms at study Week 4 (n = 36; Winstanley, Strain, & Bigelow, 2008), fluoxetine was not effective in reducing depressive symptoms.

treated with methadone. A stratified randomization procedure assigned subjects to one of four conditions: fluoxetine plus voucher incentives (FV), placebo plus voucher incentives (PV), fluoxetine without vouchers (F), and placebo without vouchers (P). Dosing of fluoxetine/placebo was double blind. Primary outcomes were treatment retention and cocaine use based on thrice-weekly urine testing. **Results:** The PV group had the longest treatment retention (M = 165 days) and lowest probability of cocaine use. The adjusted predicted probabilities of cocaine use were 65% in the P group, 60% in the F group, 56% in the FV group, and 31% in the PV group. **Conclusions:** Fluoxetine was not efficacious in reducing cocaine use in patients dually dependent on cocaine and opioids.

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Regular article

A randomized controlled trial of fluoxetine in the treatment of cocaine dependence among methadone-maintained patients

The results suggest that vouchers may not have the anticipated efficacy when patients are taking fluoxetine and that fluoxetine may actually attenuate the efficacy of vouchers. Anecdotally, clinicians report that fluoxetine may increase apathy (Hoehn-Saric, Lipsey, & McLeod, 1990), which in turn may minimize the perceived value of vouchers.

(FV), placebo plus voucher incentives (PV), fluoxetine without vouchers (F), and placebo without vouchers (P). Dosing of fluoxetine/placebo was double blind. Primary outcomes were treatment retention and cocaine use based on thrice-weekly urine testing. **Results:** The PV group had the longest treatment retention (M = 165 days) and lowest probability of cocaine use. The adjusted predicted probabilities of cocaine use were 65% in the P group, 60% in the F group, 56% in the FV group, and 31% in the PV group. **Conclusions:** Fluoxetine was not efficacious in reducing cocaine use in patients dually dependent on cocaine and opioids.

Keywords: Cocaine; Contingency management; Fluoxetine; Methadone

Fluoxetine, Smoking, and History of Major Depression: A Randomized Controlled Trial

Bonnie Spring
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University of Illinois at Chicago

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University of Illinois at Chicago and Edward Hines Jr. Veterans Affairs Hospital

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John Crayton
Edward Hines Jr. Veterans Affairs Hospital

Donald Hedeker
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The study was a randomized placebo-controlled trial testing whether fluoxetine selectively enhances cessation for smokers with a history of depression. Euthymic smokers with (H+, $n = 109$) or without (H–, $n = 138$) a history of major depression received 60 mg fluoxetine or placebo plus group behavioral quit-smoking treatment for 12 weeks. Fluoxetine initially enhanced cessation for H+ smokers ($p = .02$) but subsequently impaired cessation regardless of depressive history. Six months after quit date, fluoxetine-treated participants were 3.3 times more likely to be smoking ($p = .02$). Further research is warranted to determine why high-dose fluoxetine produces continuing effects that oppose tobacco abstinence.

Keywords: tobacco, smoking cessation, depression, fluoxetine, randomized controlled trial

Multicenter Trial of Fluoxetine as an Adjunct to Behavioral Smoking Cessation Treatment

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Denver Veterans Affairs Medical Center, Denver, Colorado

John A. Chiles
University of Texas Health Science Center at San Antonio

David B. Abrams
Brown Medical School

The authors evaluated the efficacy of fluoxetine hydrochloride (Prozac; Eli Lilly and Company, Indianapolis, IN) as an adjunct to behavioral treatment for smoking cessation. Sixteen sites randomized 989 smokers to 3 dose conditions: 10 weeks of placebo, 30 mg, or 60 mg fluoxetine per day. Smokers received 9 sessions of individualized cognitive–behavioral therapy, and biologically verified 7-day self-reported abstinence follow-ups were conducted at 1, 3, and 6 months posttreatment. Analyses assuming missing data counted as smoking observed no treatment difference in outcomes. Pattern-mixture analysis that estimates treatment effects in the presence of missing data observed enhanced quit rates associated with both the 60-mg and 30-mg doses. Results support a modest, short-term effect of fluoxetine on smoking cessation and consideration of alternative models for handling missing data.

last treatment visit were excluded from further participation in the follow-up phase because it was assumed they were smoking. We therefore conducted a survival analysis (Cox regression) on time to relapse (smoking in the past 7 days) for those participants who were abstinent at end of treatment. Time to relapse was calculated as the interval between the end-of-treatment visit and the

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this analysis as covariates. Results showed that both drug groups have an increased risk of relapse relative to the placebo group (Tables 6 and 7).

Fluoxetine treatment of cocaine-dependent patients with major depressive disorder

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Received 3 May 2000; received in revised form 31 August 2000; accepted 21 September 2000

Abstract

Sixty-eight male and female individuals with both DSM-IV diagnoses of cocaine dependence and major depressive disorder were randomly assigned to one of two medication conditions (placebo vs. 40 mg per day) as part of a double-blind, placebo-controlled clinical efficacy trial of fluoxetine for the treatment of this dual diagnosis. During the 12-week outpatient treatment phase all participants also received individual cognitive-behavioral psychotherapy targeting both cocaine use and depression. Depressive symptoms remitted as a function of time in treatment, with no significant medication effects found. Fewer cocaine positive urines were found during the first 6 weeks of treatment in the placebo group compared with the 40-mg group. Cocaine use and depressive symptoms during treatment were significantly correlated. The findings fail to support the role of fluoxetine for treatment of cocaine use and depression in dually-diagnosed patients.

Antidepressants for cocaine dependence and problematic cocaine use (Review)

Pani PP, Trogu E, Vecchi S, Amato L

Review conclusions regarding SSRI

- SSRI treated patients more likely to have adverse events vs placebo
- SSRI treated patients more likely to drop out of treatment vs placebo (including in trials where psychotherapy was offered)
- Finding held in studies in Opioid Use Disorder trials

THE COCHRANE COLLABORATION®

Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence

Steven Shoptaw [a,*], Alice Huber [b], James Peck [b], Xiaowei Yang [c], Juanmei Liu [d], Jeff Dang [a], John Roll [e], Benjamin Shapiro [f], Erin Rotheram-Fuller [a], Walter Ling [b]

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Received 9 January 2006; received in revised form 3 March 2006; accepted 6 March 2006

Abstract

Background: Methamphetamine dependence and associated medical and psychiatric concerns are significant public health issues. This project evaluated the efficacy of sertraline (50 mg bid) and contingency management (CM) for the treatment of methamphetamine dependence.

Method: In this randomized, placebo-controlled, double-blind trial, participants completed a 2-week non-medication baseline and were randomized to one of four conditions for 12 weeks: sertraline plus CM ($n = 61$), sertraline-only ($n = 59$), matching placebo plus CM ($n = 54$), or matching placebo-only ($n = 55$). All participants attended clinic thrice-weekly for data collection, medication dispensing, and relapse prevention groups. Outcomes included methamphetamine use (urine drug screening and self-reported days of use), retention (length of stay), drug craving (visual analogue scale), and mood symptoms (Beck Depression Inventory).

Results: No statistically significant main or interaction effects for sertraline or CM in reducing methamphetamine use were observed using a generalized estimating equation (GEE), although post hoc analyses showed the sertraline-only condition had significantly poorer retention than other conditions (χ^2 (3) = 8.40, $p < 0.05$). Sertraline conditions produced significantly more adverse events than placebo conditions. A significantly higher proportion of participants in CM conditions achieved three consecutive weeks of methamphetamine abstinence than those in non-CM conditions.

Conclusions: These data do not demonstrate improved outcomes for sertraline versus placebo for treatment of methamphetamine dependence; indeed, they suggest sertraline is contraindicated for methamphetamine dependence. Findings provide support for the use of contingency management for treatment of methamphetamine dependence.

A randomized double-blind, placebo-controlled trial of venlafaxine-extended release for co-occurring cannabis dependence and depressive disorders

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New York State Psychiatric Institute, Division of Substance Abuse, New York, NY, USA,[1] Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, NY, USA[2] and Department of Biostatistics, Columbia University, New York, NY, USA[3]

ABSTRACT

Aim To evaluate whether venlafaxine-extended release (VEN-XR) is an effective treatment for cannabis dependence with concurrent depressive disorders. **Design** This was a randomized, 12-week, double-blind, placebo-controlled trial of out-patients ($n = 103$) with DSM-IV cannabis dependence and major depressive disorder or dysthymia. Participants received up to 375 mg VEN-XR on a fixed-flexible schedule or placebo. All patients received weekly individual cognitive–behavioral psychotherapy that primarily targeted marijuana use. **Settings** The trial was conducted at two university research centers in the United States. **Participants** One hundred and three cannabis-dependent adults participated in the trial. **Measurements** The primary outcome measures were (i) abstinence from marijuana defined as at least two consecutive urine-confirmed abstinent weeks and (ii) improvement in depressive symptoms based on the Hamilton Depression Rating Scale. **Findings** The proportion of patients achieving a clinically significant mood improvement (50% decrease in Hamilton Depression score from baseline) was high and did not differ between groups receiving VEN-XR (63%) and placebo (69%) ($\chi_1^2 = 0.48$, $P = 0.49$). The proportion of patients achieving abstinence was low overall, but was significantly worse on VEN-XR (11.8%) compared to placebo (36.5%) ($\chi_1^2 = 7.46$, $P < 0.01$; odds ratio = 4.51, 95% confidence interval: 1.53, 13.3). Mood improvement was associated with reduction in marijuana use in the placebo group ($F_{1,179} = 30.49$, $P < 0.01$), but not the VEN-XR group ($F_{1,186} = 0.02$, $P = 0.89$). **Conclusions** For depressed, cannabis-dependent patients, venlafaxine-extended release does not appear to be effective at reducing depression and may lead to an increase in cannabis use.

Systematic Review

The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie
2020, Vol. 65(11) 749-769

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Pharmacological Treatment of Mood Disorders and Comorbid Addictions: A Systematic Review and Meta-Analysis

Traitement Pharmacologique des Troubles de L'humeur et des Dépendances Comorbides: Une Revue Systématique et une Méta-Analyse

Paul R. A. Stokes, PhD, FRCPsych[1,2,3], Tahir Jokinen, MBBS, MPhil[1], Sami Amawi, MBBCh, MSc[1], Mutahira Qureshi, MBBS[2], Muhammad Ishrat Husain, MBBS, MD(Res)[4,5], Lakshmi N. Yatham, MBBS, FRCPC[6], John Strang, FRCPsych, FMedSci[3,7], and Allan H. Young, PhD, FRCPsych[1,2,3]

Abstract

Objective: Addiction comorbidity is an important clinical challenge in mood disorders, but the best way of pharmacologically treating people with mood disorders and addictions remains unclear. The aim of this study was to assess the efficacy of pharmacological treatments for mood and addiction symptoms in people with mood disorders and addiction comorbidity.

Methods: A systematic search of placebo-controlled randomized controlled trials investigating the effects of pharmacological treatments in people with bipolar disorder (BD) or major depressive disorder (MDD), and comorbid addictions was performed. Treatment-related effects on mood and addiction measures were assessed in a meta-analysis, which also estimated risks of participant dropout and

Results: A total of 32 studies
placebo for improving manic sy
−0.29 to −0.02; $P = 0.03$) but
significantly improved manic sym
(SMD = −0.07; 95% CI, −0.23
depressive symptoms in MDD (
symptoms (SMD = −0.58; 95%
treatments had no effect (SMD =

treatment effects in BD. Eggers regression test indicated significant publication bias ($P = 0.02$).

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

ABSTRACT

BACKGROUND

Evidence-based medicine is valuable to the extent that the evidence base is complete and unbiased. Selective publication of clinical trials — and the outcomes within those trials — can lead to unrealistic estimates of drug effectiveness and alter the apparent risk–benefit ratio.

METHODS

We obtained reviews from the Food and Drug Administration (FDA) for studies of 12 antidepressant agents involving 12,564 patients. We conducted a systematic lit-

From the Departments of Psychiatry (E.H.T., A.M.M.) and Pharmacology (E.H.T.), Oregon Health and Science University; and the Behavioral Health and Neurosciences Division, Portland Veterans Affairs Medical Center (E.H.T., A.M.M., R.A.T.) — both in Portland, OR; the Department of Psychology, Kent State University, Kent, OH (E.L.); the Department of Psychology, University of California–

National Institutes of Health

Predicting Alcoholics' Treatment Responses to a Selective Serotonin Re-uptake Inhibitor (SSRI)

ClinicalTrials.gov ID NCT00249405

Sponsor University of Cincinnati

Information provided by University of Cincinnati

Last Update Posted 2010-11-03

Study Details | Table View | **No Results Posted** | Record History

On this page

- Results Overview
- Publications
- More Information

Results Overview

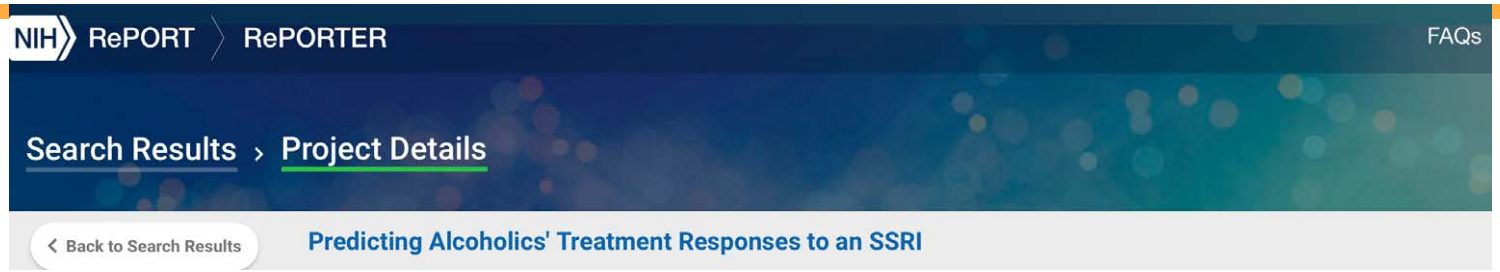
No Study Results Posted on ClinicalTrials.gov for this Study

Study results have not been submitted. This may be because the study isn't done, the deadline for submitting results has not passed, or this study isn't required to submit results.

Recruitment Status	Actual Primary Completion Date	Actual Study Completion Date
Completed	2010-10	2010-10

Publications

The person responsible for entering information about the study voluntarily provides these publications. These may be about anything related to the study.



- The 5-HTTLPR did not broadly predict which AD individuals would respond to a trial of citalopram to promote reductions in drinking
- These results differ to some extent from the findings of Kranzler et al.[1] and Pettinati et al.[3] by demonstrating that a patient's drinking goal, and not alcoholism typology *per se,* may influence treatment response to SSRIs
- Participants whose goal it was to abstain from drinking tended to have fewer days abstinent on citalopram compared with placebo

Poster presented at the 33rd Annual RSA Scientific Meeting, San Antonio, Texas, June 2010.

What about antipsychotics?

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Can antipsychotic treatment contribute to drug addiction in schizophrenia?

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ABSTRACT

Individuals with schizophrenia are at very high risk for drug abuse and addiction. Patients with a coexisting drug problem fare worse than patients who do not use drugs, and are also more difficult to treat. Current hypotheses cannot adequately account for why patients with schizophrenia so often have a co-morbid drug problem. I present here a complementary hypothesis based on evidence showing that chronic exposure to antipsychotic medications can induce supersensitivity within the brain's dopamine systems, and that this in turn can enhance the rewarding and incentive motivational effects of drugs and reward cues. At the neurobiological level, these effects of antipsychotics are potentially linked to antipsychotic-induced increases in the striatal levels of dopamine D2 receptors and D2 receptors in a high-affinity state for dopamine, particularly at postsynaptic sites. Antipsychotic-induced dopamine supersensitivity and enhanced reward function are not inevitable consequences of prolonged antipsychotic treatment. At least two parameters appear to promote these effects; the use of antipsychotics of the typical class, and continuous rather than intermittent antipsychotic exposure, such that silencing of dopaminergic neurotransmission via D2/3 receptors is unremitting. Thus, by inducing forms of neural plasticity that facilitate the ability of drugs and reward cues to gain control over behaviour, some currently used treatment strategies with typical antipsychotics might contribute to compulsive drug seeking and drug taking behaviours in vulnerable schizophrenia patients.

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Neurosci Biobehav Rev. 2021 January ; 120: 123–158. doi:10.1016/j.neubiorev.2020.11.004.

Using pharmacological manipulations to study the role of dopamine in human reward functioning: A review of studies in healthy adults

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Addressing Obesity in Patients Taking Antipsychotics

April 28, 2021
Mehrul Hasnain, MD
Psychiatric Times, Vol 38, Issue 4, Volume 04,

Antipsychotic-induced weight gain evolves over time, leads to chronic complications, and is very difficult to reverse. Pharmacologic interventions used to tackle weight gain are modestly effective and worth considering in certain cases.

Modulating tobacco smoking rates by dopaminergic stimulation and blockade

Nicholas H. Caskey, Murray E. Jarvik, William C. Wirshing, Damian C. Madsen, Paula N. Iwamoto-Schaap, Naomi I. Eisenberger, Lorena Huerta, Scott M. Terrace, Richard E. Olmstead

[Received 20 April 2000; accepted 20 June 2001]

This study was designed to demonstrate that dopaminergic stimulation would result in decreased smoking behavior and nicotine intake, whereas dopaminergic blockade would result in increased smoking behavior and nicotine intake, in the same subjects. In prior human studies, a dopaminergic antagonist, haloperidol, increased

Aripiprazole maintenance increases smoked cocaine self-administration in humans

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Abstract

Rationale—Partial dopamine receptor agonists have been proposed as candidate pharmacotherapies for cocaine dependence.

Objective—This 42-day, within-subject, human laboratory study assessed how maintenance on aripiprazole, a partial D_2 receptor agonist, influenced smoked cocaine self-administration, cardiovascular measures, subjective effects, and cocaine craving in nontreatment-seeking, cocaine-dependent volunteers.

Methods—In order to achieve steady-state concentrations, participants (n=8 men) were administered placebo and aripiprazole (15 mg/day) capsules in counter-balanced order for 21 days. A smoked cocaine dose–response curve (0, 12, 25, 50 mg) was determined twice under placebo and aripiprazole maintenance. Sessions comprised a "sample" trial, when participants smoked the cocaine dose available that session, and five choice trials, when they responded on a progressive-ratio schedule of reinforcement to receive the cocaine dose or receive $5.00.

Aripiprazole mai
administration in

Margaret Haney, **Eric Ru**
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Division on Substance Ab
New York, NY 10032, US

Margaret Haney: mh235@colur

Abstract

Rationale—Partial do
pharmacotherapies for

Objective—This 42-d
aripiprazole, a partial D
cardiovascular measure
dependent volunteers.

Methods—In order to
administered placebo a
A smoked cocaine dose
and aripiprazole mainte
cocaine dose available
ratio schedule of reinfo

The American Journal of Psychiatry

BRIEF REPORT

A Comparison of Aripiprazole, Methylphenidate, and Placebo for Amphetamine Dependence

Objective: Problems related to illegal amphetamine use have become a major public health issue in many developed countries. To date, evidence on the effectiveness of psychosocial treatments has remained modest, and no pharmacotherapy has proven effective for amphetamine dependence. **Method:** Individuals meeting DSM-IV criteria for intravenous amphetamine dependence (N=53) were randomly assigned to receive aripiprazole (15 mg/day), slow-release methylphenidate (54 mg/day), or placebo for 20 weeks. The study was terminated prematurely due to unexpected results of interim analysis. An intention-to-treat analysis was used. The primary outcome measure was the proportion of amphetamine-positive urine samples. **Results:** Patients allocated to aripiprazole had significantly more amphetamine-positive urine samples than patients in the placebo group (odds ratio=3.77, 95% CI=1.55–9.18), whereas patients who received methylphenidate had significantly fewer amphetamine-positive urine samples than patients who had received placebo (odds ratio=0.46, 95% CI=0.26–0.81). **Conclusions:** Methylphenidate is an effective treatment for reducing intravenous drug use in patients with severe amphetamine dependence.

FLUPENTHIXOL DECANOATE AND RELAPSE PREVENTION IN ALCOHOLICS: RESULTS FROM A PLACEBO-CONTROLLED STUDY

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(*Received* 27 *March* 2000; *in revised form* 9 *January* 2001; *accepted* 6 *February* 2001)

Abstract — Flupenthixol, with its broad receptor profile, interacts with a variety of dopamine and serotonin binding sites which are important in the neurobiology of alcohol dependence. Its pharmacology, together with encouraging results from both animal studies and clinical trials with cocaine users, led us to postulate that flupenthixol would significantly prevent relapse in detoxified alcohol-dependent individuals. We conducted a prospective, randomized, double-blind, placebo-controlled, multi-centre trial with two parallel groups and appropriate statistical evaluation. Subjects met criteria for moderate to severe alcohol dependence (DSM-III-R), without any concomitant psychiatric disorder. After complete detoxification, 281 women and men received either 10 mg of flupenthixol decanoate or placebo as i.m. injection every second week for 6 months on an out-patient basis, followed by 6 months of follow-up. Efficacy was based on absolute abstinence, with relapse being defined as consumption of any alcohol after inclusion in the study. In contrast to the hypothesis, flupenthixol did not reduce, but was associated with more, relapses. Though well tolerated, relapse rates after 6 months of treatment were 85.2% (flupenthixol) versus 65.5% (placebo), a highly significant difference from the medication. Flupenthixol was also inferior to placebo with regard to other secondary criteria of efficacy (cumulative abstinence duration, relapse rate after 12 months). These results indicate that a 10 mg dose of flupenthixol decanoate does not have a beneficial effect on abstinence maintenance in alcohol-dependent individuals.

Benzodiazepines as a mainstay in alcohol withdrawal?

Addiction

RESEARCH REPORT

doi:10.1111/j.1360-0443.2012.03975.x

Correlates of benzodiazepine dependence in the Netherlands Study of Depression and Anxiety

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ABSTRACT

Aims Benzodiazepines (BZDs) are effective in the short term against anxiety and insomnia. However, some BZD users develop BZD dependence after a relatively short period of time. Therefore, we aimed to identify the risk factors of BZD dependence. **Design** An observational cohort study. **Setting** The Netherlands. **Participants** Four hundred and one BZD users of the 2981 participants of the Netherlands Study of Depression and Anxiety (NESDA) were included. **Measurements** Socio-demographic, physical, psychological, addiction-related and BZD use-related characteristics were investigated as possible correlates of BZD dependence severity. Dependence severity was measured by the three subscales of the Benzodiazepine Self-Report Questionnaire, comprising problematic use, preoccupation and lack of compliance. **Findings** In multivariate analyses, problematic use was associated with more GP contacts in the past 6 months ($\beta = 0.170$, $P = 0.001$) and severity of insomnia ($\beta = 0.145$, $P = 0.004$). Preoccupation was related to anxiety severity ($\beta = 0.194$, $P = 0.001$), antidepressant use ($\beta = 0.197$, $P < 0.001$), alcohol dependence ($\beta = 0.185$,

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Characterization of benzodiazepine misuse and comorbidities in patients with alcohol use disorder

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Abstract

Background: Due to the frequent presence of anxious symptoms and sleep disorders, benzodiazepines (BZD) are often prescribed to patients with alcohol use disorder (AUD).

Objectives: To assess BZD misuse and psychiatric comorbidities in patients with AUD.

Methods: This prospective, monocentric study included all adult patients with AUD hospitalized in a French addiction unit for alcohol withdrawal from November 2017 to May 2018.

Results: Among the 153 patients included, 75 (49%) were using BZD at the time of their hospitalization. Duration of alcohol addiction was longer in BZD users: (33 ± 27 years vs. 29 ± 11 years; $P = 0.001$). BZD misuse was noted in 27 patients consuming benzodiazepines (36% of BZD users and 18% of all included patients), mainly increase in the dose (on average, 3 ± 4 times

Low-dose diazepam primes motivation for alcohol and alcohol-related semantic networks in problem drinkers

C. X. Poulos[a,b] and M. Zack[a,c,d]

Considerable research with animals indicates that the GABA–benzodiazepine (BZ) system plays a key role in alcohol reinforcement. However, only limited research appears to have assessed this issue directly in humans. The present study investigated whether low-dose diazepam would cross-prime motivation for alcohol in problem drinkers. Twelve male problem drinkers (Alcohol Dependence Scale; ADS score ≥ 9) received oral diazepam (5 mg) and placebo, in a counterbalanced manner on separate sessions. There were three measures of primed motivation for alcohol: self-reported desire for alcohol, consumption of placebo beer in an ostensible taste test procedure, and automatically executed vocal reading responses to Alcohol versus Neutral words on a computer-based task. Diazepam significantly increased beer consumption, and produced a marginally significant increase in reported desire for alcohol. On the reading task, diazepam significantly decreased response latency to Alcohol words relative to Neutral words. Latency to Alcohol words correlated significantly with beer consumption under the drug. Moreover, response latency to Alcohol words under the drug also predicted ADS scores. Thus, severity of dependence was directly linked with vulnerability to a BZ priming effect on motivation for alcohol. These findings provide direct evidence that the GABA–BZ system plays an important role in alcohol reinforcement in problem drinkers. *Behavioural Pharmacology* 15:503–512 © 2004 Lippincott Williams & Wilkins.

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Keywords: alcohol, benzodiazepines, priming, motivation, semantic memory networks, human

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A Double-Blind Trial of Gabapentin Versus Lorazepam in the Treatment of Alcohol Withdrawal

Hugh Myrick, Robert Malcolm, Patrick K. Randall, Elizabeth Boyle, Raymond F. Anton, Howard C. Becker, and Carrie L. Randall

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.

Several common justifications that contribute to polypharmacy (i.e. what I previously taught)

- Effective pharmacotherapies for concurrent disorders are critical to improve AUD treatment outcomes
- This may be particularly true among poly-substance use users (e.g. nicotine, cocaine) where pharmacotherapy can be most effective
- Medications should be routinely prescribed for a minimum of several months as a therapeutic trial given low risk if found to be ineffective
- Combining concurrent disorders and AUD pharmacotherapy with psychosocial treatments (e.g. relapse prevention training, CBT, etc) is most effective

Final Thoughts

- Polypharmacy (often for AUD symptom management) is common among persons with AUD and others with SUD
- A possible explanation is that negative trials are often unpublished and/or poorly appreciated by prescribers (who often have few other options)*
- An EBM approach highlights the importance of focusing on substance use as a major underlying contributor to mental health symptoms
- It highlights the need to address medications with poor evidence of benefit and also prioritize non-medication based mental health interventions
- An EBM approach also suggest looking for medication adverse effects in patients with increased alcohol after certain medication is prescribed
- And, of course, the overall need to build a more evidence-based and accessible system of care for persons with alcohol and other substance use disorder

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Questions?