Best Evidence Webinar: Addressing medications that are ineffective and potentially harmful for patients with alcohol and other substance use disorders

Evan Wood, MD, PhD, FRCPC, FASAM

Professor & Canada Research Chair

in Addiction Medicine,

University of British Columbia

I would like to acknowledge that I am presenting today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

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

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**

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 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

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

cmaj
CANADIAN MEDICAL ASSOCIATION JOURNAL

Financial contribution:

Health Canada Santé Canada

CRISM

A Typical Case

- A 48-year-old married, employed father presents to his family MD complaining of ”drinking too much” and “feeling down for a long time”
- After some conversation about reducing drinking, an SSRI antidepressant is started for low mood
- The patient returns without improvement and complaining of poor sleep. The SSRI dose is increased; trazodone is added to support sleep
- The patient ultimately presents for inpatient withdrawal management due to ongoing severe alcohol use disorder

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

Naltrexone (reduction of heavy drinking)

Acamprosate (Abstinence)

“What about all the other medications commonly prescribed?”

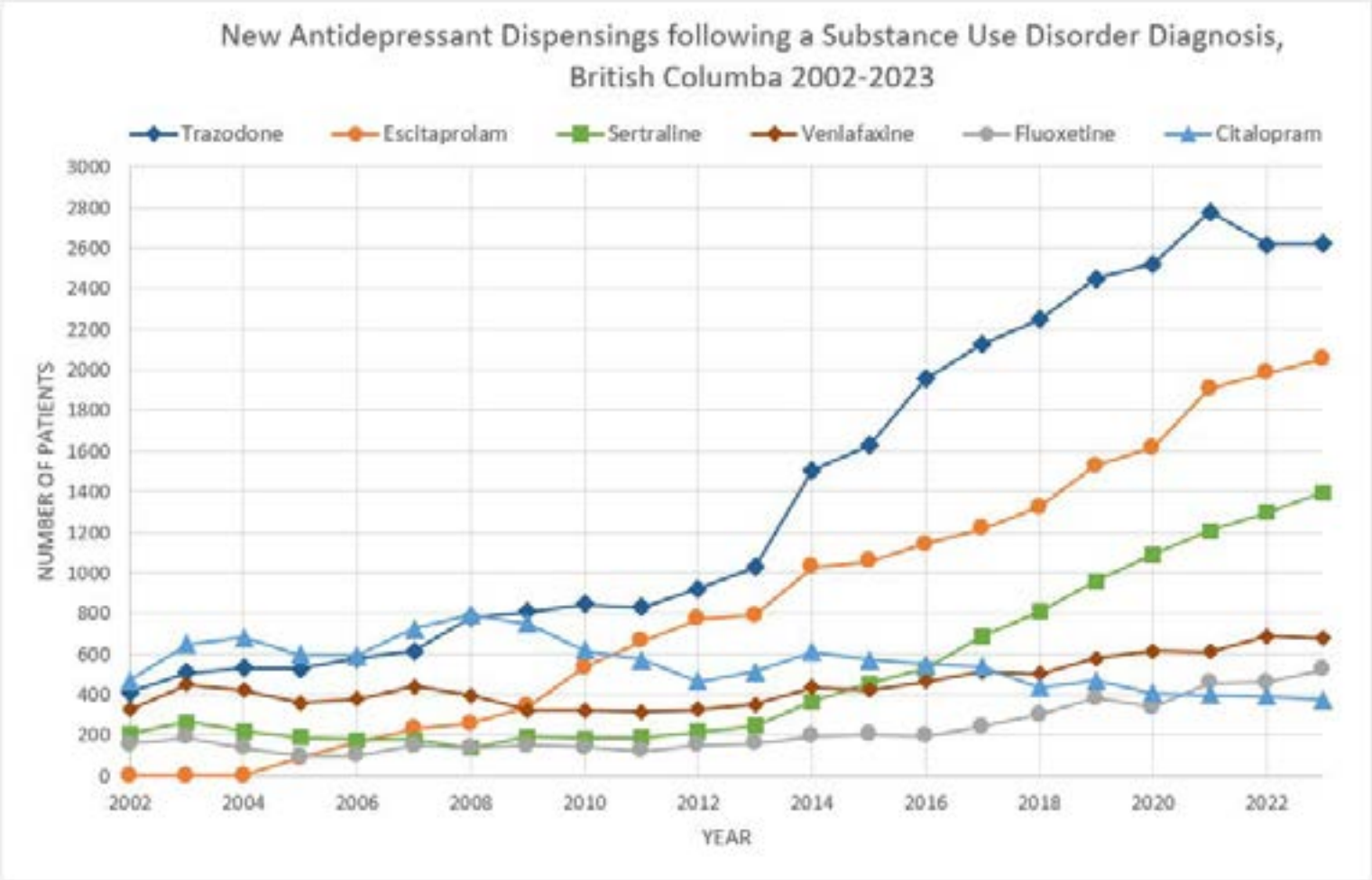
Table 2: Summary of recommendations

	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

Several common “Truisms” that contribute to polypharmacy (i.e. what I previously taught)

- Antidepressants for concurrent disorders are critical to improve AUD treatment outcomes
- This may be particularly true among poly-substance users (e.g. nicotine, cocaine) where antidepressants are effective
- Medications should be routinely prescribed for a minimum of several months given low risk if found to be ineffective
- Combining antidepressants with psychosocial treatments (e.g. relapse prevention counselling, CBT, etc) is ideal

Antidepressants in Substance Use Disorder (SUD)



A Couple of Problems with these "Truisms"…

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

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

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

−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

formed. 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

What about the Cochrane Reviews?

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

Version published: 20 January 2015 Version history

https://doi.org/10.1002/14651858.CD007505.pub2

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

Version published: 24 April 2018 Version history

https://doi.org/10.1002/14651858.CD008581.pub2

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.

"We found low quality evidence.. (for) treatment of people with co-occurring depression and alcohol dependence… Moreover, most of these positive effects were no longer significant when studies with a high risk of bias were excluded."

Characteristics of Excluded Studies

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

A Couple of Problems with these "Truisms"...

1. Serotonergic antidepressants are not particularly effective for treating mental health symptoms in those with AUD.
2. While often unseen elsewhere in medicine, the research supporting routine antidepressant use is questioned in EBM circles*

therapeutics letter
July - August 2016

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Study 329: Why is it so important?

Study 329 is a GlaxoSmithKline (GSK) sponsored trial with 22 academic authors that compared paroxetine, imipramine, and placebo for adolescent depression. In this trial 275 adolescents with major depression were randomized in a double-blind fashion to paroxetine (93), imipramine (95) or placebo (87) for 8 weeks. Those who completed 8 weeks were studied in a 6-month continuation phase.

Published 8-week results (2001)[1]: Compared with placebo,

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

Emma Maund *PhD student*[1], Britta Tendal *postdoctoral researcher*[1], Asbjørn Hróbjartsson *senior researcher*[1], Karsten Juhl Jørgensen *senior researcher*[1], Andreas Lundh *physician*[1 2], Jeppe Schroll *PhD student*[1], Peter C Gøtzsche *Professor*[1]

[1]Nordic Cochrane Centre, Rigshospitalet Dept 7811, Copenhagen, Denmark; [2]Department of Infectious Diseases, Hvidovre University Hospital, Kettegårds Allé 30, 2650 Hvidovre, Denmark

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.

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

Emma Maund *PhD student*[1], Britta Tendal *postdoctoral researcher*[1], Asbjørn Hróbjartsson *senior researcher*[1], Karsten Juhl Jørgensen *senior researcher*[1], Andreas Lundh *physician*[1,2], Jeppe Schroll *PhD student*[1], Peter C Gøtzsche *Professor*[1]

[1]Nordic Cochrane Centre, Rigshospitalet Dept 7811, Copenhagen, Denmark; [2]Department of Infectious Diseases, Hvidovre University Hospital, Kettegårds Allé 30, 2650 Hvidovre, Denmark

Abstract

in journal articles and Lilly trial registry reports, respectively. We also found publication bias in relation to beneficial effects

"Clinical study reports contained extensive data on major harms that were unavailable in journal articles..."

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

Lancet 2018; 391: 1357–66

Published Online February 21, 2018 http://dx.doi.org/10.1016/S0140-6736(17)32802-7

See Comment page 1333

*Joint first authors

Department of Psychiatry, University of Oxford, Oxford, UK (A Cipriani MD, L Z Atkinson MSc, H G Ruhe PhD, Prof J R Geddes MD); **Oxford Health NHS Foundation Trust** (A Cipriani, Prof J R Geddes) **and**

BMJ Open

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

To cite: Munkholm K, Paludan-Müller AS, Boesen K. Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis. *BMJ Open* 2019;**9**:e024886. doi:10.1136/bmjopen-2018-024886

► Prepublication history and additional material for this paper are available online. To view, please visit the journal (http://dx.doi.org/10.1136/bmjopen-2018-024886).

Received 19 June 2018
Revised 18 October 2018
Accepted 8 May 2019

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

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. *

ELSEVIER

Journal of Clinical Epidemiology 70 (2016) 155–163

Journal of Clinical Epidemiology

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

Shanil Ebrahim[a,b,c,d,e], Sheena Bance[f], Abha Athale[g], Cindy Malachowski[h], John P.A. Ioannidis[a,b,h,i,*]

[a]Stanford Prevention Research Center, Department of Medicine, Stanford University, 1265 Welch Road, 3rd Floor, Stanford, CA 94305, USA
[b]Meta-Research Innovation Center at Stanford (METRICS), Stanford University, 1265 Welch Road, Stanford, CA 94305, USA
[c]Department of Clinical Epidemiology & Biostatistics, McMaster University, 1200 Main Street West, Room 2C, Hamilton, Ontario L8S 4K1, Canada
[d]Department of Anesthesia, McMaster University, 1200 Main Street West, HSC 2U1, Hamilton, Ontario L8S 4K1, Canada
[e]Department of Anaesthesia and Pain Medicine, Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G 1X8, Canada
[f]Department of Applied Psychology and Human Development, Ontario Institute for Studies in Education, University of Toronto, 252 Bloor Street West, Toronto, Ontario M5S 1V6, Canada
[g]Department of Rehabilitation Science, University of Toronto, 500 University Ave, Toronto, Ontario M5G 1V7, Canada
[h]Department of Health Research and Policy, Stanford University School of Medicine, Redwood Building T152, 150 Governor's Lane, Stanford, CA 94305, USA
[i]Department of Statistics, Stanford University School of Humanities and Sciences, 390 Serra Mall, Stanford, CA 94305, USA

Accepted 26 August 2015; Published online 21 September 2015

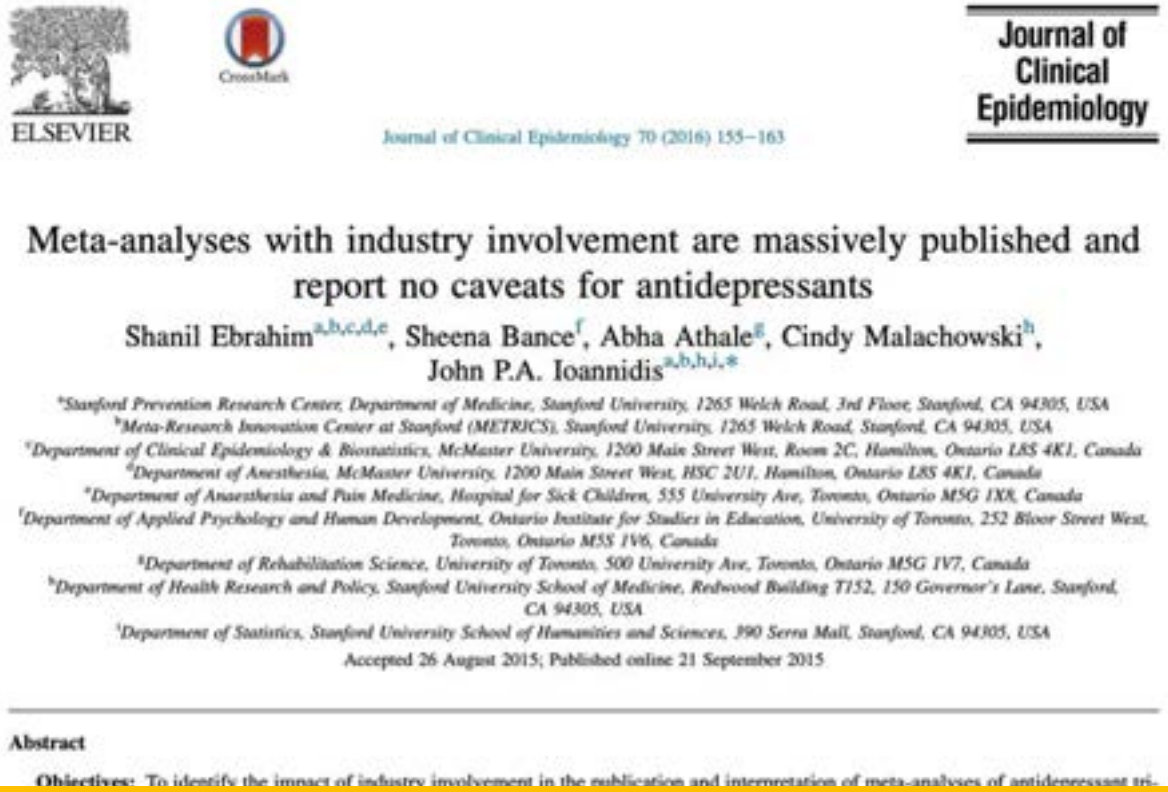
Abstract

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.



ELSEVIER

Journal of Clinical Epidemiology 70 (2016) 155–163

Journal of Clinical Epidemiology

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

Shanil Ebrahim[a,b,c,d,e], Sheena Bance[f], Abha Athale[g], Cindy Malachowski[h], John P.A. Ioannidis[a,b,h,i,*]

[a]Stanford Prevention Research Center, Department of Medicine, Stanford University, 1265 Welch Road, 3rd Floor, Stanford, CA 94305, USA
[b]Meta-Research Innovation Center at Stanford (METRICS), Stanford University, 1265 Welch Road, Stanford, CA 94305, USA
[c]Department of Clinical Epidemiology & Biostatistics, McMaster University, 1200 Main Street West, Room 2C, Hamilton, Ontario L8S 4K1, Canada
[d]Department of Anesthesia, McMaster University, 1200 Main Street West, HSC 2U1, Hamilton, Ontario L8S 4K1, Canada
[e]Department of Anaesthesia and Pain Medicine, Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G 1X8, Canada
[f]Department of Applied Psychology and Human Development, Ontario Institute for Studies in Education, University of Toronto, 252 Bloor Street West, Toronto, Ontario M5S 1V6, Canada
[g]Department of Rehabilitation Science, University of Toronto, 500 University Ave, Toronto, Ontario M5G 1V7, Canada
[h]Department of Health Research and Policy, Stanford University School of Medicine, Redwood Building T152, 150 Governor's Lane, Stanford, CA 94305, USA
[i]Department of Statistics, Stanford University School of Humanities and Sciences, 390 Serra Mall, Stanford, CA 94305, USA

Accepted 26 August 2015; Published online 21 September 2015

Abstract

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

"There is a massive production of meta-analyses of antidepressants authored or linked to the industry, and they almost never report any caveats…"

A Couple of Problems with these truisms when serotonergic antidepressants are used in AUD

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

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

Mark Zimmerman [1], Heather L Clark [2], Matthew D Multach [2], Emily Walsh [2], Lia K Rosenstein [2], Douglas Gazarian [2]

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.

"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

Francisco Alén[1,2*], Laura Orio[2*], Miguel Á Gorriti[1], Raquel Gómez de Heras[1], María Teresa Ramírez-López[1], Miguel Ángel Pozo[3] and Fernando Rodríguez de Fonseca[2]

[1] *Departamento de Psicobiología, Facultad de Psicología, Universidad Complutense de Madrid, Spain*

[2] *Fundación IMABIS, Laboratorio de Medicina Regenerativa, Hospital Regional Universitario Carlos Haya, Málaga, Spain*

[3] *Instituto Pluridisciplinar, Universidad Complutense de Madrid, Spain*

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

IOS Press

Ninety-three cases of alcohol dependence following SSRI treatment

Louise Brookwell[a], Carys Hogan[a], David Healy[a,*] and Derelie Mangin[b]
[a]*North Wales Department of Psychological Medicine, Bangor, Wales, UK*
[b]*David Braley & Nancy Gordon Chair of Family Medicine, Department of Family Medicine, McMaster University, ON, Canada*

Received 12 February 2014
Accepted 9 March 2014

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.

IOS Press

Ninety-three cases of alcohol dependence following SSRI treatment

Louise Brookwell[a], Carys Hogan[a], David Healy[a,*] and Derelie Mangin[b]
[a]*North Wales Department of Psychological Medicine, Bangor, Wales, UK*
[b]*David Braley & Nancy Gordon Chair of Family Medicine, Department of Family Medicine, McMaster University, ON, Canada*

Received 12 February 2014
Accepted 9 March 2014

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.

"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."

What about double blind placebo-controlled trials?

0145-6008/96/2004-0788$03.00/0
Alcoholism: Clinical and Experimental Research

Vol. 20, No. 4
June 1996

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.

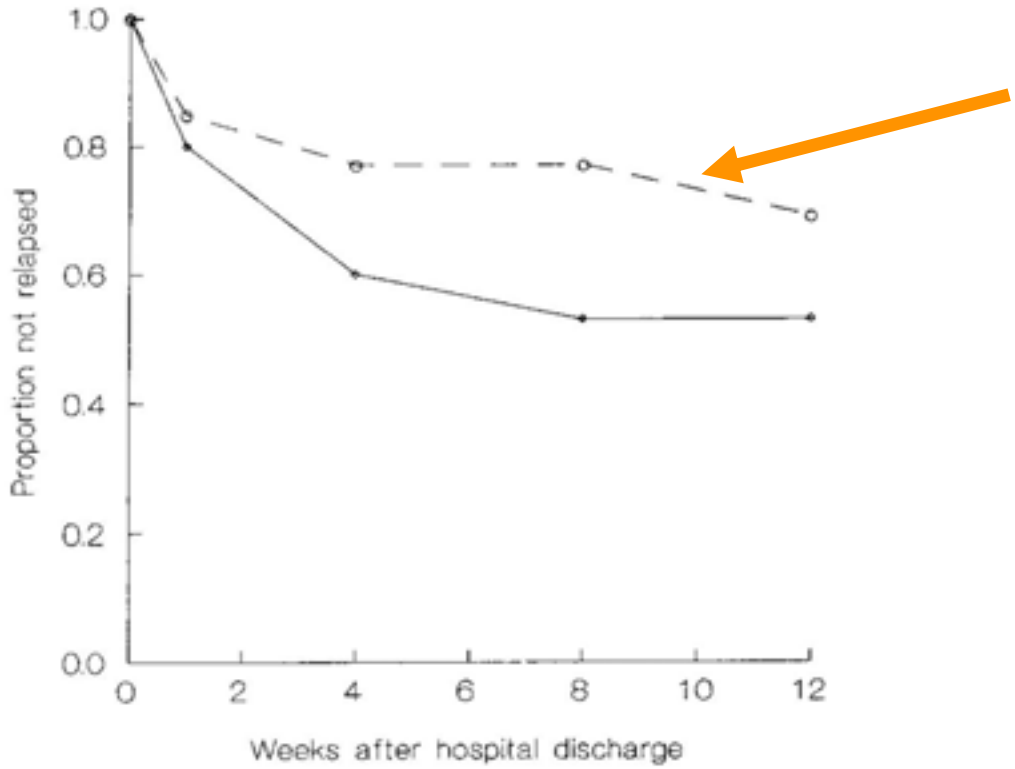
Key Words: Alcoholism, Fluoxetine, Selective Serotonin Reuptake Inhibitors.

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

782 Fluoxetine (N=15) vs placebo (N=13) for AUD



Less relapses with placebo

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

0145-6008/96/2009-1534$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 20, No. 9
December 1996

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 plac 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 measures 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.

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

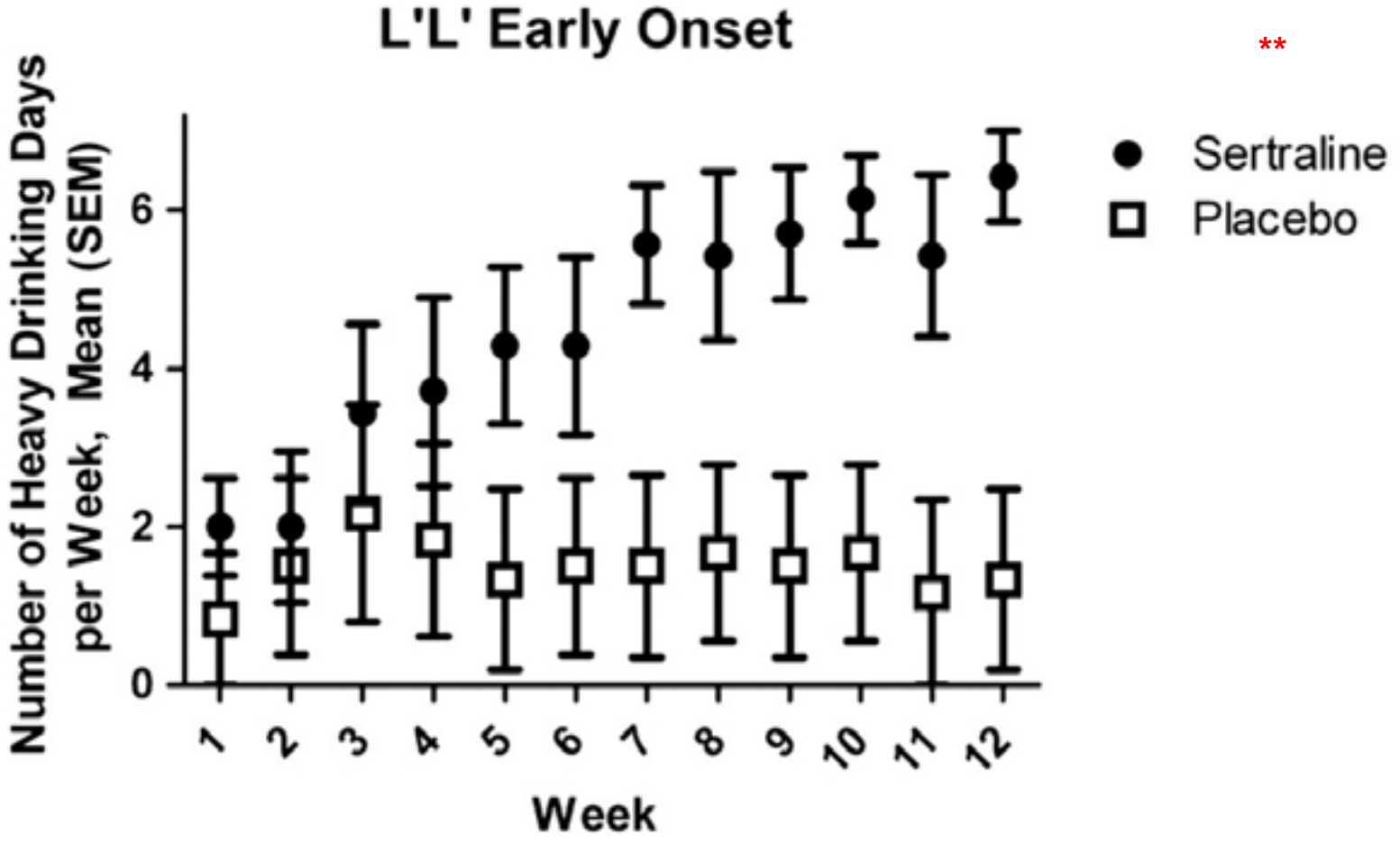
Moderation by Age of Onset and 5-Hydroxytryptamine Transporter-Linked Promoter Region Genotype

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

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.

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

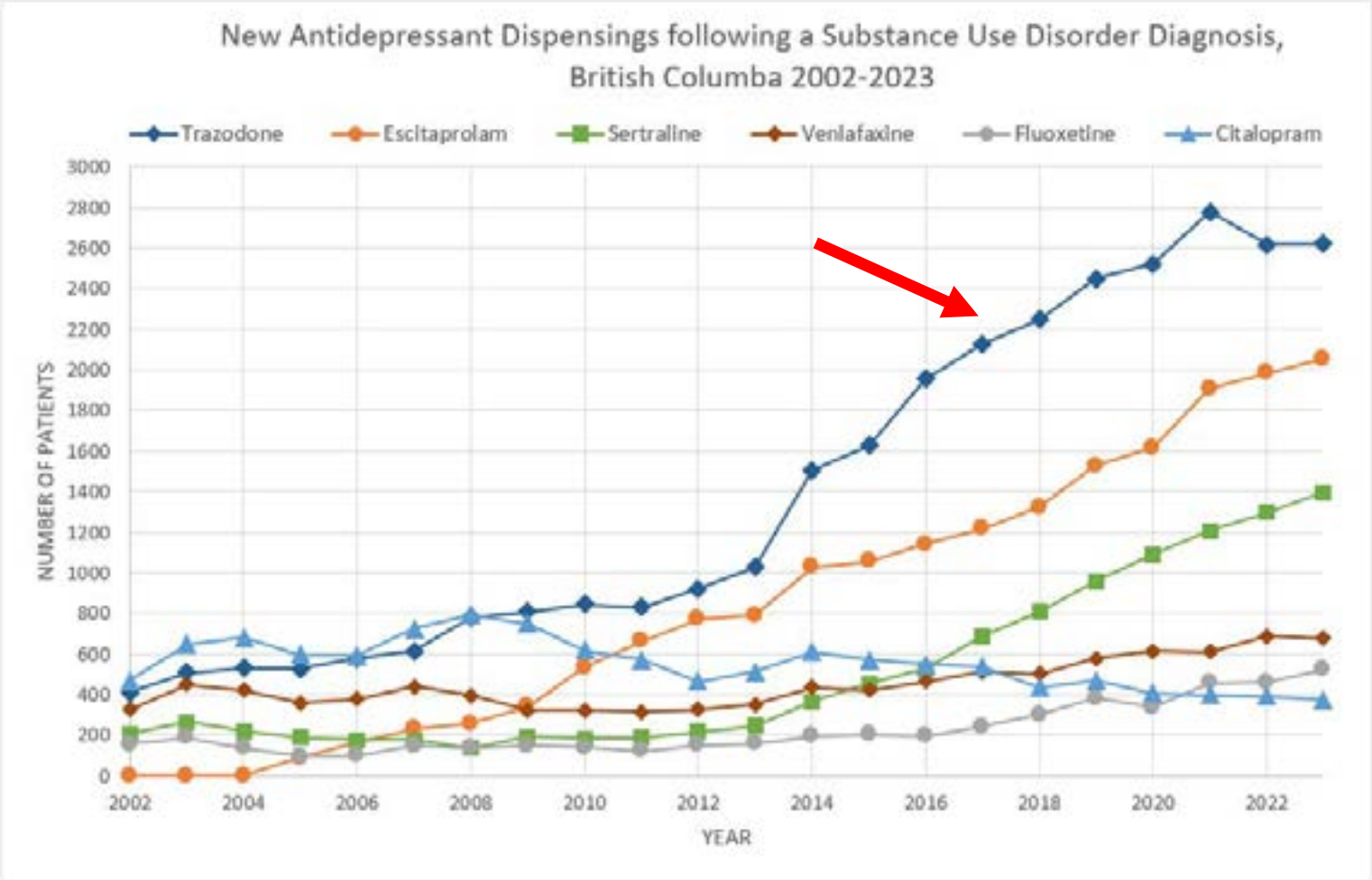
Background: Previous research on the use of selective serotonin reuptake inhibitors (SSRIs) as a treatment for alcohol dependence has yielded mixed results. Depression has been shown to be a predictor of relapse and poor outcome following treatment, and it has been hypothesized that SSRIs would be beneficial 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

"The results suggest that the use of SSRIs among depressed and non-depressed alcohol-dependent individuals in early recovery, prior to the onset of abstinence, may be contraindicated."

What about Trazodone?

Antidepressants in Substance Use Disorder (SUD)



Alcoholism: Clinical and Experimental Research

Vol. 32, No. 9
September 2008

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.

Alcoholism: Clinical and Experimental Research

Vol. 32, No. 9
September 2008

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

"Trazodone, despite a short-term benefit on sleep quality, might impede improvements in alcohol consumption in the post-detoxification period and lead to increased drinking when stopped."

Advocacy for Trazodone?

0090-9556/98/2606-0572-575$02.00/0
DRUG METABOLISM AND DISPOSITION

Vol. 26, No. 6
Printed in U.S.A.

DRUG METABOLISM & DISPOSITION

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

SUSAN ROTZINGER,[1] JIAN FANG, AND GLEN B. BAKER

Neurochemical Research Unit, Department of Psychiatry and Faculty of Pharmacy and Pharmaceutical Sciences, and Division of Neuroscience, University of Alberta

(Received October 15, 1997; accepted March 2, 1998)

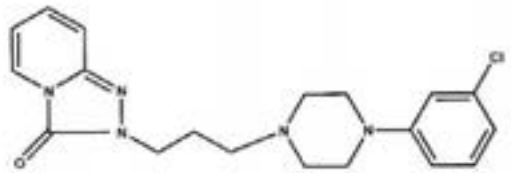
This paper is available online at http://www.dmd.org

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)[7] 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

Neuropsychopharmacology (2011) 36, 1178–1186

www.neuropsychopharmacology.org

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

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]

[a]*Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH 45220, USA*
[b]*Linder Center of HOPE, Mason, OH 45040, USA*
[c]*Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD, 21224, USA*
[d]*Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA 23235, USA*

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

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],

.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.

Keywords: Cocaine; Contingency management; Fluoxetine; Methadone

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

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 treatment of cocaine-dependent patients with major depressive disorder

Joy M. Schmitz *, Patricia Averill, Angela L. Stotts, F. Gerard Moeller, Howard M. Rhoades, John Grabowski

Department of Psychiatry and Behavioral Sciences, Substance Abuse Research Center, University of Texas Medical School Houston, Houston, TX 77030, USA

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.

Fluoxetine treatment of cocaine-dependent patients with major depressive disorder

Joy M. Schmitz *, Patricia Averill, Angela L. Stotts, F. Gerard Moeller, Howard M. Rhoades, John Grabowski

Department of Psychiatry and Behavioral Sciences, Substance Abuse Research Center, University of Texas Medical School Houston, Houston, TX 77030, USA

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,

"Fewer cocaine positive urines were found during the first 6 weeks of treatment in the placebo group compared with the 40mg group..."

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]

[a] *Center for Health Promotion and Disease Prevention, Department of Family Medicine, David Geffen School of Medicine at UCLA, 10880 Wilshire Blvd, Suite 1800, Los Angeles, CA 90024, United States*

[b] *Integrated Substance Abuse Programs, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, 11075 Santa Monica Blvd, Suite 200, Los Angeles, CA 90025, United States*

[c] *Department of Public Health Sciences One Shields Avenue, TB-168, University of California, Davis, CA 95616-8638, United States*

[d] *Department of Psychology-Measurement, UCLA, Box 951563, 1285 FH, Los Angeles, CA 90095-1563, United States*

[e] *WSU-Spokane Health Sciences, Washington State University, P.O. Box 1495, Spokane, WA 99210-1495, United States*

[f] *Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, C-8 mailroom, Los Angeles, CA 90024, United States*

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.

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]

[a] *Center for Health Promotion and Disease Prevention, Department of Family Medicine, David Geffen School of Medicine at UCLA, 10880 Wilshire Blvd, Suite 1800, Los Angeles, CA 90024, United States*
[b] *Integrated Substance Abuse Programs, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, 11075 Santa Monica Blvd, Suite 200, Los Angeles, CA 90025, United States*
[c] *Department of Public Health Sciences One Shields Avenue, TB-168, University of California, Davis, CA 95616-8638, United States*
[d] *Department of Psychology-Measurement, UCLA, Box 951563, 1285 FH, Los Angeles, CA 90095-1563, United States*
[e] *WSU-Spokane Health Sciences, Washington State University, P.O. Box 1495, Spokane, WA 99210-1495, United States*
[f] *Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, C-8 mailroom, Los Angeles, CA 90024, United States*

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.

"These data do not demonstrate improved outcomes for sertraline… indeed they suggest sertraline is contraindicated for methamphetamine dependence."

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

Frances R. Levin[1,2], John Mariani[1,2], Daniel J. Brooks[1], Martina Pavlicova[3], Edward V. Nunes[1,2], Vito Agosti[2], Adam Bisaga[1,2], Maria A. Sullivan[1,2] & Kenneth M. Carpenter[1,2]

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.

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

Frances R. Levin[1,2], John Mariani[1,2], Daniel J. Brooks[1], Martina Pavlicova[3], Edward V. Nunes[1,2], Vito Agosti[2], Adam Bisaga[1,2], Maria A. Sullivan[1,2] & Kenneth M. Carpenter[1,2]

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

"For depressed cannabis-dependent patients, venlafaxine-extended release does not appear to be effective at reducing depression and my 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

Article reuse guidelines:
sagepub.com/journals-permissions
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

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

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

- 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.

Several common “Truisms” that contribute to polypharmacy (i.e. what I previously taught)

- Antidepressants for concurrent disorders are critical to improve AUD treatment outcomes
- This may be particularly true among poly-substance users (e.g. nicotine, cocaine) where antidepressants are effective
- Medications should be routinely prescribed for a minimum of several months given low risk if found to be ineffective
- Combining antidepressants with psychosocial treatments (e.g. relapse prevention counselling, CBT, etc) is ideal

Returning to a Typical Case

- The use of an SSRI is unlikely to provide benefit for mood or anxiety according to meta-analyses
- Longstanding evidence including from the largest RCTs in this population demonstrate increased alcohol use
- Similarly trazodone has similar risks for increased drinking that may persist after it is stopped
- These observations are seen in other substance use disorders where serotonergic antidepressants have unproven benefit and may induce worse outcomes

Final Thoughts

- Polypharmacy is very common among persons with AUD and other SUD who are often being treated for side effects of substance use
- The likely explanation is that negative trials are often unpublished, poorly represented in reviews, and overall poorly appreciated by prescribers
- An EBM approach suggest that we prioritize safer mental health interventions for common comorbidities
- It highlights the need to be aware of medications with poor evidence of benefit and also be vigilant for side effects
- When serotonergic antidepressants are used, prescribers should be advised to warn patients with (substance use disorder) about unproven benefits and potential for adverse effects (including increased substance use)

Acknowledgements

CRISM National AUD Guideline Committee and Funders:

Health Canada (Substance Use and Addictions Program 2021-HQ-000066) and in-kind contributions from the British Columbia Centre on Substance Use and the Centre for Addiction and Mental Health.

Therapeutics Initiative including Editor of the Therapeutics Letter

Health Canada via CIHR and the Canada Research Chairs Program

Questions?