Eli Lilly – F.O.I. REQUEST

103 Healy long term strategy.

Thank you for the message outlining your strategy to counteract Dr David Healy's claims re: Prozac and violence.

Send a letter to Healy designed to get him to stop discussing a study that he has never done.

Have a third party expert in the audience at BAP to ask Healy questions when he presents.

Just last Thursday Healy was quoted in a Cincinnati paper saying Prozac causes violence and suicide…X has asked that we go back to legal and determine if we can sue Healy under UK law.

104 Huge turn out… Good talk. Lesson no sponsor if Healy present in future.

Worldwide Development
Pfizer Inc
50 Pequot Avenue
New London, CT 06320

Global Research & Development

July 26, 2004

Robert J. Temple, M.D.
Director, Office of Drug Evaluation I (HFD-101)
Rockwall 2
5515 Security Ln
Rockville, MD 20852

Dear Dr. Temple:

This letter responds to the arguments set out in Dr. David Healy's letter to the Food and Drug Administration ("FDA"), through Peter J. Pitts, dated February 19, 2004. As described in detail in this response, we are gravely concerned that the many erroneous statements, unsupported contentions, and data distortions in Dr. Healy's letter will, if not examined, exposed, and rejected by the FDA, endanger large numbers of citizens suffering from serious, often life-threatening mental disorders and illnesses.

Dr Healy has distorted and mischaracterized the evidence… many erroneous statements, unsupported contentions and data distortions

Dr Healy has been hired by lawyers representing civil-litigation plaintiffs and criminal defendants to criticise SSRIs in at least 8 cases. Although he is a psychiatrist and reader at the University of North Wales, he is primarily known for his work as a medical historian. He has little scientific experience in conducting and interpreting the results of controlled clinical research.

Before becoming a litigation expert witness testifying against SSRI manufacturers, Dr Healy published views opposite to those he now espouses on the question of whether SSRIs induce suicide.

But there is still money to be made, cashing in on credentials and providing distorted interpretations of the literature for a hefty fee. DH is now out pounding the pavement hustling business.

J Coyne June 3rd 2000

We should ask: what is H up to? Apparently he is bypassing experimental design and peer review and running his "experiment" and putting this claim in a newspaper but without key details of his "study"? It fits with his solicitation of business as an expert witness with a predictable position for sale. It does not fit with ethical guidelines that are generally accepted by serious medical researchers

J Coyne June 5th 2000

Having followed the controversy concerning DH and the UoT with .. fascination, I am convinced that .. the key persons involved never familiarized themselves with Dr. H's record. This includes whoever was responsible for making the original offer to him, the newspaper who declared him a world class researcher .. Dr. H has almost no published scientific research

The "research" which has caused all the furor in Toronto involved giving antidepressants to 20 underlings... The colleagues were undoubtedly aware of his hypothesis that antidepressants cause suicide because he had made a reputation and lots of money making that claim before he collected his data. All of the usual scientific controls including a placebo control were missing from this "experiment". The whole project was ethically and scientifically suspect.

I think the fuss, if there is to be any, should be about his being deemed a researcher or made an offer in the first place.

J Coyne Letter: Globe and Mail Sept 7th 2001

Well, finally the H study was uncovered, having been buried away beyond scrutiny because no original source was given and it was not in a MEDLINE reviewed journal. We find that the study was bogus or incompetent in its design because only it has only 20 subjects and no placebo condition were included in what we are asked to believe was a scientific study of quality of life. No statistical power for the stated purpose of the study. The subjects were colleagues and underlings of Dr. H and the study postdated his widely publicized claims for his hypothesis. Is this scientifically appropriate or ethical?

Was there a conflict of interest on Healy's part? Do you see an ethical issue or an outright scam here (I guess incompetence is a defense against the latter charge)?

J Coyne May 1st 2001

Dear Dr Healy,

Thank you very much for all your hard work on this article. I'm afraid we've run into a legal wall with our libel lawyer reluctant for us to publish your piece… I remain supportive of publication but obviously can't do this against legal advice.

Our lawyer has several questions that he wants us to address at this stage. He isn't ruling out publication, but we need to reassure him about the facts first.

Best wishes,

XX

Editor Big 4 Journal

He had not only BEEN an expert witness when he published that article, he was ACTIVELY a witness in unresolved civil suit in which it was crucial that he be able to cite data for his otherwise unsubstantiated position that ssri's make people suicidal. Releasing the paper to accomplish that was both timely and sleazy, and all the more so because he did not disclose his relevant financial interests in the study having a particular outcome. His testimony and soliciting of law suits was quite germane to any effort to make sense of his bizarre report and I doubt many readers understood the connection. Your claim that the connection was so obvious that no mention was needed is hypocritical horseshit.

Incidently, when it is convenient, Healy accepts considerable money from drug companies, more than most people I know. that is not mentioned either.

J Coyne Sept 11th 2001

On Sun, 16 Sep 2001, James Coyne wrote:

Dr. Miller, although you sometimes personally have intelligent things to say on sscpnet, some of your postings convey the critical faculties of a broken lawn chair.

I am referring in particular to your postings concerning my role in the reporting in the Canadian press of the rescinding of an offer to H from the U of Toronto.

Wed Nov 7th 2001

I wonder if Dr. Elliott would like to revise his account of the Hastings Center caper? Might he concede that his bad judgment may have been damaging to the credibility of the Hastings Center Report and may have given H the added claim of having "results" published in Hastings Center Report in his promotion of the interests of an Evil Pharmaceutical Company and his own consulting activities?

Since Dr Coyne has felt the need to post a diatribe against me - a UK journalist - on this list, I am posting my reply to him. I hope that will be the end of the matter.

Dear Dr Coyne

For the record, I have no connection whatsoever with the Scientologists. If you looked further back you might find an article which was an attempt to expose their cult in the UK. I am not able to prevent them putting my articles on any website they have (I have never seen this site and was not aware they had done so). They have mailed me various things about drugs, but I always bin them.

I'm sorry you take exception to what I wrote about you. I felt it was fair. We obviously disagree. I note that you didn't reply to my second email, asking what you meant when you said you had received "hate mail" from Healy supporters. If you could have substantiated your allegations, I would have been happy to include those too.

I make no apology for having written plenty of stories about Dr Healy. I have done so because I find his allegations about the SSRIs disturbing and because I have yet to receive convincing evidence that he is wrong. When and if I do receive such evidence I will cease to write about these issues.

Can I say that I take exception to what I consider your bullying and intimidatory behaviour.

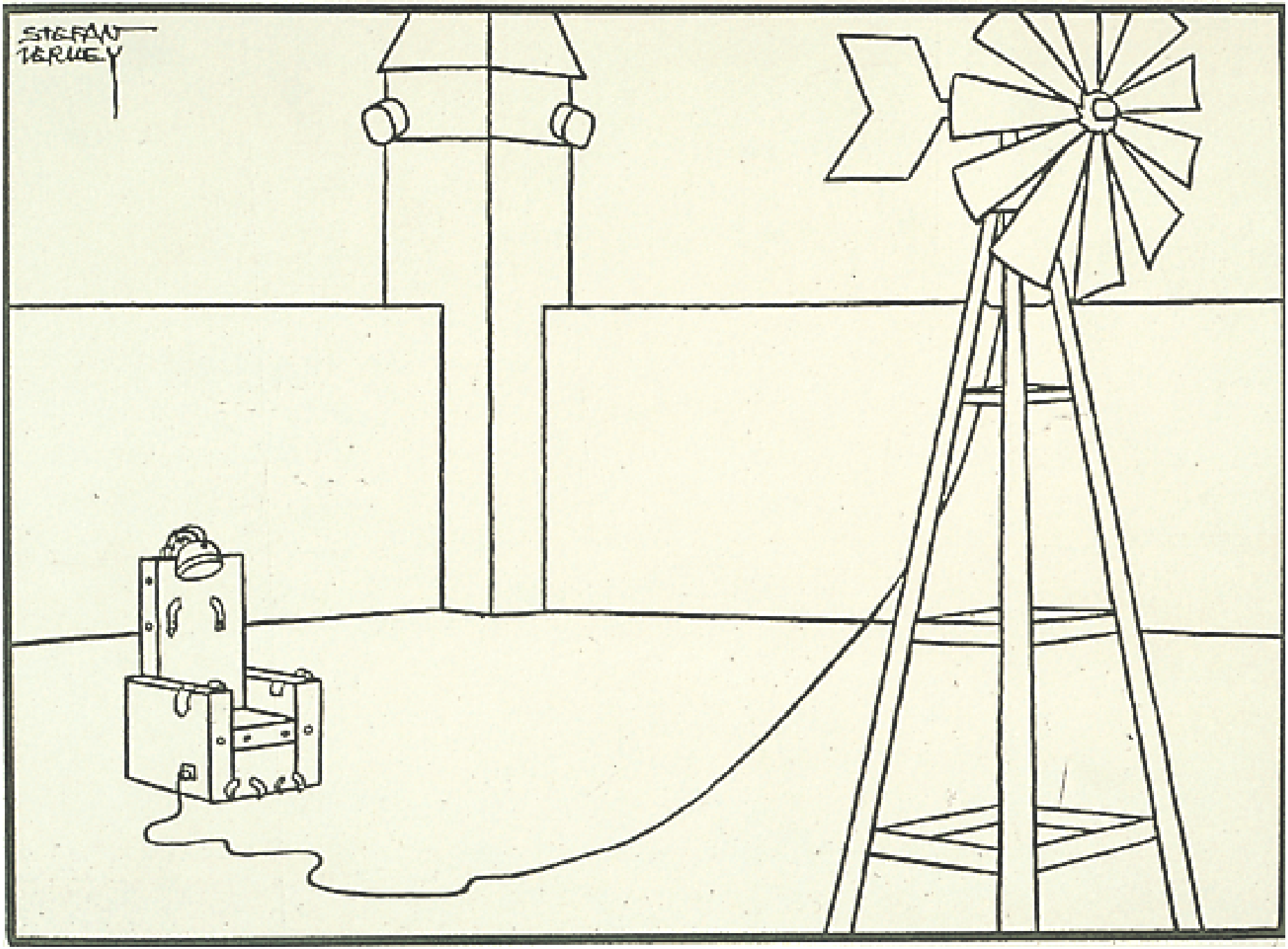
Sarah Boseley May 23rd 2002

To: Society for a Scientific Clinical Psychology SSCPNET@listserv.it.northwestern.edu 2005
From: James C Coyne jcoyne@mail.med.upenn.edu
Subject: new UK guidelines for antidepressant use in children

… [SB and DA] share a penchant for professing to be vigilant about conflict of interests, but nonetheless promoting the paid testimony of David Healy, who, for fees greater than 30,000 Euros will show up as an expert witness armed with his junk science "normal volunteers" study and data that have been repeatedly shown to be cooked.

Date: Sat, 24 Sep 2005 17:49:54 -0400
To: "David Goldstein" davidgoldstein715@msn.com
From: James C Coyne jcoyne@mail.med.upenn.edu
Subject: Re: Xavier Amador, PhD. clinical psychologist and the Abu Ghraib courtmartials
Cc: sscpnet@listserv.it.northwestern.edu

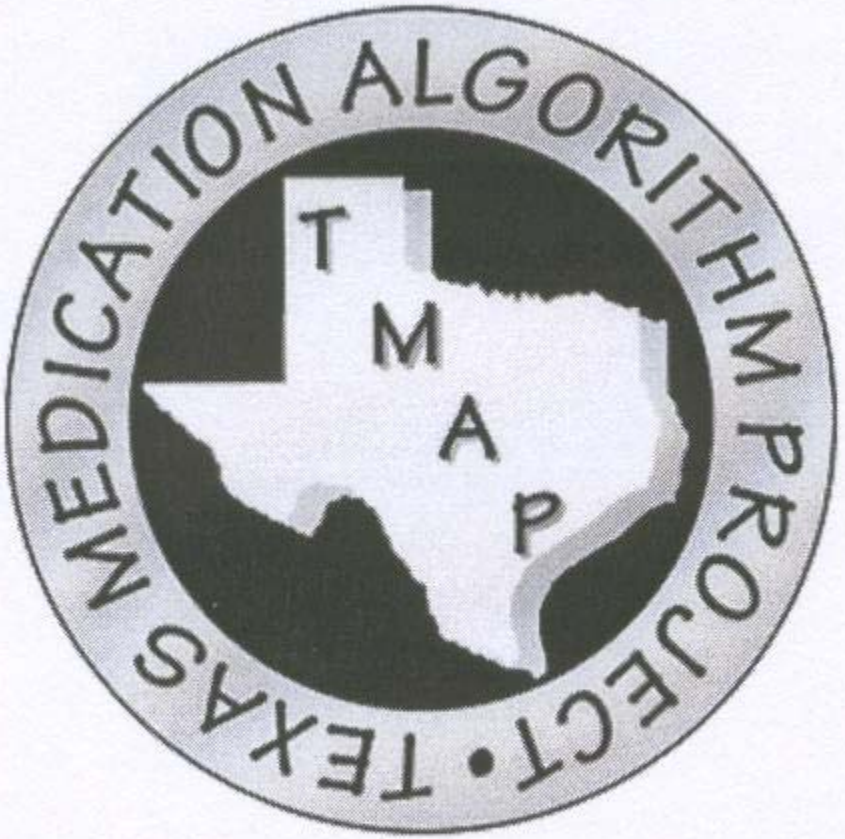
A little bit of googling of Amador's name will provide some fascinating quotes from him. there are lots. he is quite a publicity hound. He is a lot like David Healy, although I am not aware of Amador cooking up data. he seems to rely on the projection of some sort of special clinical expertise.


STEFAN
TARUCZY

We would consider any advertisement or promotion labeling for RISPERDAL false, misleading or lacking fair balance under Section 502 of the Act if there is a presentation of data that conveys the impression that Risperidone is superior to haloperidol or any other marketed antipsychotic drug product with regard to safety or effectiveness.

FDA Review of Risperdal 1993

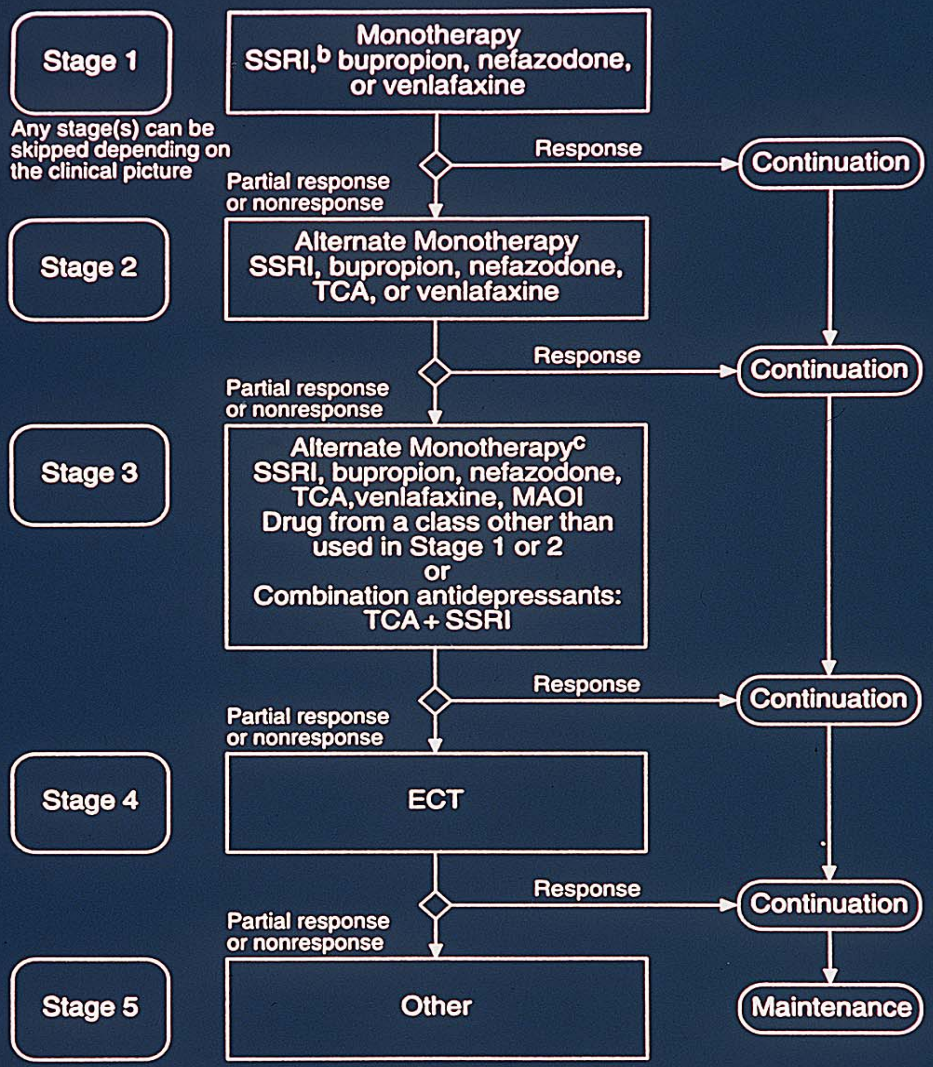
Texas Medication Algorithm Project



Click here to continue

MHMR Home

Figure 1. Strategies for the Treatment of Major Depressive Disorder Without Psychotic Features[a]



[a]The Texas Medication Algorithm Project (TMAP) algorithms are in the public domain, and these figures may be reproduced without permission, but with appropriate citation. Abbreviations:
ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor,
TCA = tricyclic antidepressant.
[b]SSRIs preferred.
[c]Consider TCA or venlafaxine if not tried.

CONSENSUS STATEMENT ON SCHIZOPHRENIA STANDARDS IN CARE FOR MAINTENANCE THERAPY AND POORLY RESPONDING/TREATMENT-INTOLERANT PATIENTS

Mortimer A[1], Healy D[2], Gray R[3], Peveler R[4], Pratt P[5], Sharma T[3], Turner T[6]

[1]University of Hull, Hull; [2]Department of Psychological Medicine, Bangor; [3]Institute of Psychiatry, London; [4]Royal South Hants Hospital, Southampton; [5]Community Health, Sheffield; [6]Homerton Hospital, London

Evidential consensus views of experts from a meeting in November 1997 – revision of the 1996 Consensus Statement on Schizophrenia Standards in Care

Introduction

Over the last decade, several 'atypical' antipsychotics have been introduced for the treatment of schizophrenia. In 1996, the Consensus Statement on Schizophrenia Standards in Care was developed to reflect changed attitudes towards the treatment of schizophrenia, with the advent of clozapine and risperidone. Subsequently, several other 'atypical' antipsychotics – olanzapine, sertindole, quetiapine and amisulpride – were introduced further expanding treatment choices for clinicians in the UK. Hence, a second group of psychiatrists, pharmacists and nurses met to update the first Consensus Statement in Schizophrenia Standards in Care, using a combination of literature review and expert consensus opinion – an evidential approach. This revision reflects the wider choice of drugs available and the greater emphasis placed on medication counselling and psychosocial interventions in the long-term treatment of schizophrenia.

Methodology

A group of psychiatrists, pharmacists and nurses met to discuss the drug treatment of schizophrenia in maintenance therapy and poorly responding/treatment-intolerant patients. The aims of this collaboration were:

- To discuss new and existing treatment regimens
- To devise drug treatment guidelines which combine effective treatment with minimum side effects
- To recommend the minimum standards in care for individual patient groups.

These guidelines include information which is relevant to decision-making processes and provide a basic, logical framework which can be modified according to local needs and preferences.

Maintenance therapy

Definition of patients on maintenance therapy

Maintenance therapy refers to the long-term control of a previously good or adequate response to treatment, with continuous assessment and active management of side effects (especially tardive dyskinesia) through pharmacotherapy, medication counselling (e.g. compliance therapy) and outreach programmes.

Drug treatment algorithm (Figure 1)

Patients in the acute stage of treatment are usually on higher doses than will be necessary for maintenance treatment. During maintenance therapy, it is important that, wherever possible, a patient is only receiving one antipsychotic and that the dose has been individually titrated to the minimum effective level for that patient. Oral preparations are generally preferred by patients, but if non-compliance is a problem depot medication should be considered *(Davis et al, 1994)*. Choice of medication should be made in consultation with the patient, the care team, and, if appropriate, the family or relevant carers.

If patients are well on oral medication, they should remain on the lowest dose possible. The likelihood of relapse may be reduced by implementing programmes of self-medication in inpatients; this allows patients to become used to taking drugs at a set time of day while being monitored by hospital staff. Compliance therapy and family psychoeducation within the first six months are also critical for improving compliance.

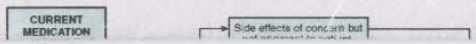
Ideally, patients should be given one antipsychotic of established efficacy, for which there is extensive clinical experience, and with a low side-effect profile. During maintenance therapy, the typical side effects of any drugs given may include weight gain, dysphoria, akathisia, sedation, sexual dysfunction and cognitive impairment. Side effects should be actively monitored during maintenance treatment, usually by a community psychiatric nurse (CPN), using a standard assessment tool such as the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS; *Day et al, 1995)* or the Extrapyramidal Symptoms Rating Scale (ESRS). If deterioration begins, the causes should be assessed and the patient's mental state monitored. Use of a standardised instrument like the Early Signs Scale (ESS) *(Birchwood et al, 1989)*, which measures changes in key symptoms both phenomenologically (self-report) and behaviourally (observer report), can help identify a possible relapse. Assessment should be done as frequently as practicable, for example monthly. Early intervention to prevent a full-blown relapse is then possible.

Often a short course of adjunctive medication to treat the patient during a temporary crisis, for example using benzodiazepines for excessive agitation or sleeplessness, rather than increasing antipsychotic dose, will be adequate *(Thompson, 1994)*. Ideally, the need for anticholinergic medication should be avoided in maintenance therapy because anticholinergics may compromise cognitive function. Some clinicians also believe that anticholinergics may, paradoxically, worsen negative symptoms.

If there is no obvious cause for the relapse, a temporary increase in antipsychotic dose may be necessary. Once symptoms start to improve, the dose should be reduced to the minimal effective level for that patient. This allows for another dose increase to be made should it become necessary in the future.

If non-adherence to treatment is suspected, the reasons for this should be investigated and addressed. If the reason for non-adherence is the emergence of side effects that affect the patient's daily functioning and quality of life such as extrapyramidal side effects (EPS), oversedation, marked weight gain or sexual dysfunction, a change of medication is indicated (refer to *treatment-intolerant patients – drug treatment algorithm)*.

Patients should be reviewed at least annually to monitor mental state, personal function/behavioural problems, cognitive function, cardiovascular health and general health (diet, smoking etc.). Preferably, such assessments should be done in the patient's own home to allow a comprehensive view of the patient's behaviour and social functioning as well as ensuring a meeting with a member of the community care team (social worker, CPN, GP, etc.). On completion, the care team should review the patient's medication and adjust as necessary.



Poor-response and treatment-intolerant patients

Definitions

Poor-response patients

These are patients with poorly controlled positive and/or negative symptoms (defined by team judgement for individual patients) after 12 weeks of treatment on an antipsychotic medication (either an atypical or a conventional antipsychotic) at doses which do not exceed British National Formulary (BNF) guidelines.

Treatment-intolerant patients

Patients who cannot tolerate a therapeutic dose (below the upper limit of BNF guidelines) of an antipsychotic without unacceptable and uncontrollable side effects or a worsening of psychosis.

Poor response patients – drug-treatment algorithm (Figure 2)

Before a patient can be defined as a poor responder to antipsychotic medication, the diagnosis of schizophrenia must be re-assessed to rule out the possibility of an alternative illness, such as borderline personality disorder, affective disorder, organic psychosis, or independent/co-morbid substance abuse, where more appropriate treatment should be used. Assessment for substance abuse is most commonly done using a urine drug screen. Furthermore, adherence to treatment should be assessed to determine that non-compliance is not the reason for the poor response. This can be done by nursing observation, measurement of prolactin levels and discussion with carers, family and the patient. If it transpires that the patient is not adhering to treatment, then their reasons for this need to be investigated. If, for example, the patient is intolerant to side effects of their medication, they should be offered an alternative antipsychotic with a more acceptable side-effect profile (refer to *treatment-intolerant patients – drug treatment algorithm)*. Genotyping can sometimes help to identify poor response and treatment-intolerant patients – people with low levels of CYP2D6 enzymes may be far more susceptible to side effects.

receive a trial of at least two marketed neuroleptics before being considered for clozapine treatment.

If a patient has failed a 12-week trial of an atypical antipsychotic and has previously been unresponsive to at least one other antipsychotic the switch to clozapine should be considered. Some clinicians may try another atypical antipsychotic first, but there is no evidence base for this. On the basis of data from a study by Meltzer et al (1989), the panel recommended a minimum trial of clozapine of six months before trying any other unused options. When a patient reaches the 'unused options' stage of the algorithm, the evidence base of any recommendations is negligible – some clinicians will add in an adjunctive treatment, e.g. lithium for mood elevation, benzodiazepine for psychotic agitation or anticonvulsants for psychomotor overactivity.

The panel gave consideration to the issue of how 'poor response' might be defined for patients who have 'failed' a trial of a conventional neuroleptic, an atypical antipsychotic other than clozapine and then a minimum six-month trial of clozapine. While such patients may not be 'well', it is possible that they are better than if they came off medication altogether. Clinicians should consider what the goal of treatment is for these patients in conjunction with the wishes of these patients and their families.

Finally, the panel stated that it is good clinical practice, and especially pertinent for poor-response patients, to specify at the outset of treatment what a reasonable period might be for a treatment trial of a given therapy with a given patient, how the outcome of treatment will be judged, what the side effects are expected to be, and what options might be considered should the treatment fail. At all stages of this treatment algorithm, tolerance to treatment and non-drug factors should be considered as part of the assessment of poor response. If at any point the side effects render the patient intolerant to treatment, refer to *treatment-intolerant patients – drug treatment algorithm.*

Treatment-intolerant patients – drug treatment algorithm (Figure 3)

Patients who fall into this category have responded to their antipsychotic but are unable to maintain that response without suffering unacceptable side effects or experiencing a worsening of their psychosis because of dose reduction to ameliorate side effects. However, intolerance to the side effects of antipsychotic medication is often overlooked – when reasons for non-compliance are sought, patients cite side effects far more

Technology Appraisal Guidance - No. 43

NHS

National Institute for Clinical Excellence

Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia

June 2002

CATALYST
Healthcare Communications Ltd

PHARMACOECONOMIC EVALUATION OF RISPERIDONE

IN THE LONG-TERM TREATMENT OF CHRONIC SCHIZOPHRENIA

STRICTLY CONFIDENTIAL

PREPARED FOR JANSSEN-CILAG

BY

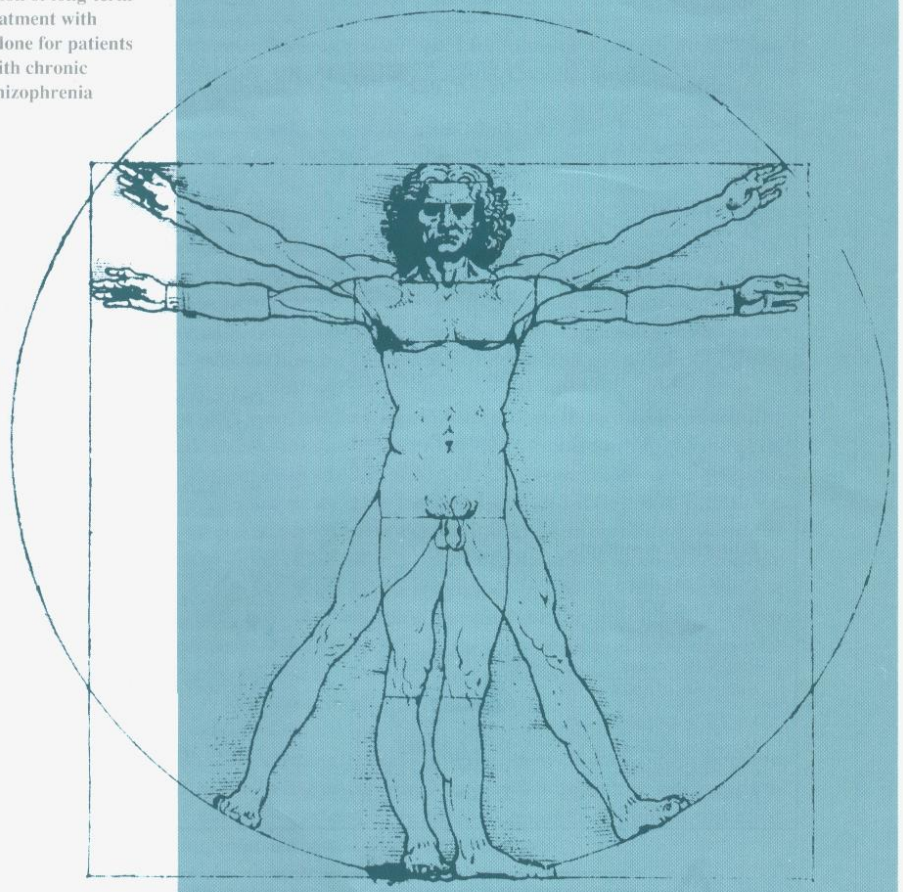
CATALYST HEALTHCARE COMMUNICATIONS LTD

ISSN 0962-1423

1996 Volume 10
Pages 59-67

The British Journal of Medical Economics

Pharmacoeconomic evaluation of long-term treatment with risperidone for patients with chronic schizophrenia



BROOKWOOD MEDICAL PUBLICATIONS

The Cost-Effectiveness of Olanzapine Compared with Haloperidol in the Treatment of Schizophrenia in the UK

Final Report
Prepared for Lilly Industries Limited

3 December 1996

Stephen Almond, BA
Owen O'Donnell, BA,MSc,D.Phil

Personal Social Services Research Unit
University of Kent at Canterbury

WORLDWIDE PUBLICATIONS STATUS UPDATE

ZOLOFT®
(Sertraline HCl)

PREPARED BY
CURRENT MEDICAL DIRECTIONS, INC
JANUARY 29, 1999

Current Medical Directions

“to deliver scientifically accurate information strategically developed for specific target audiences”

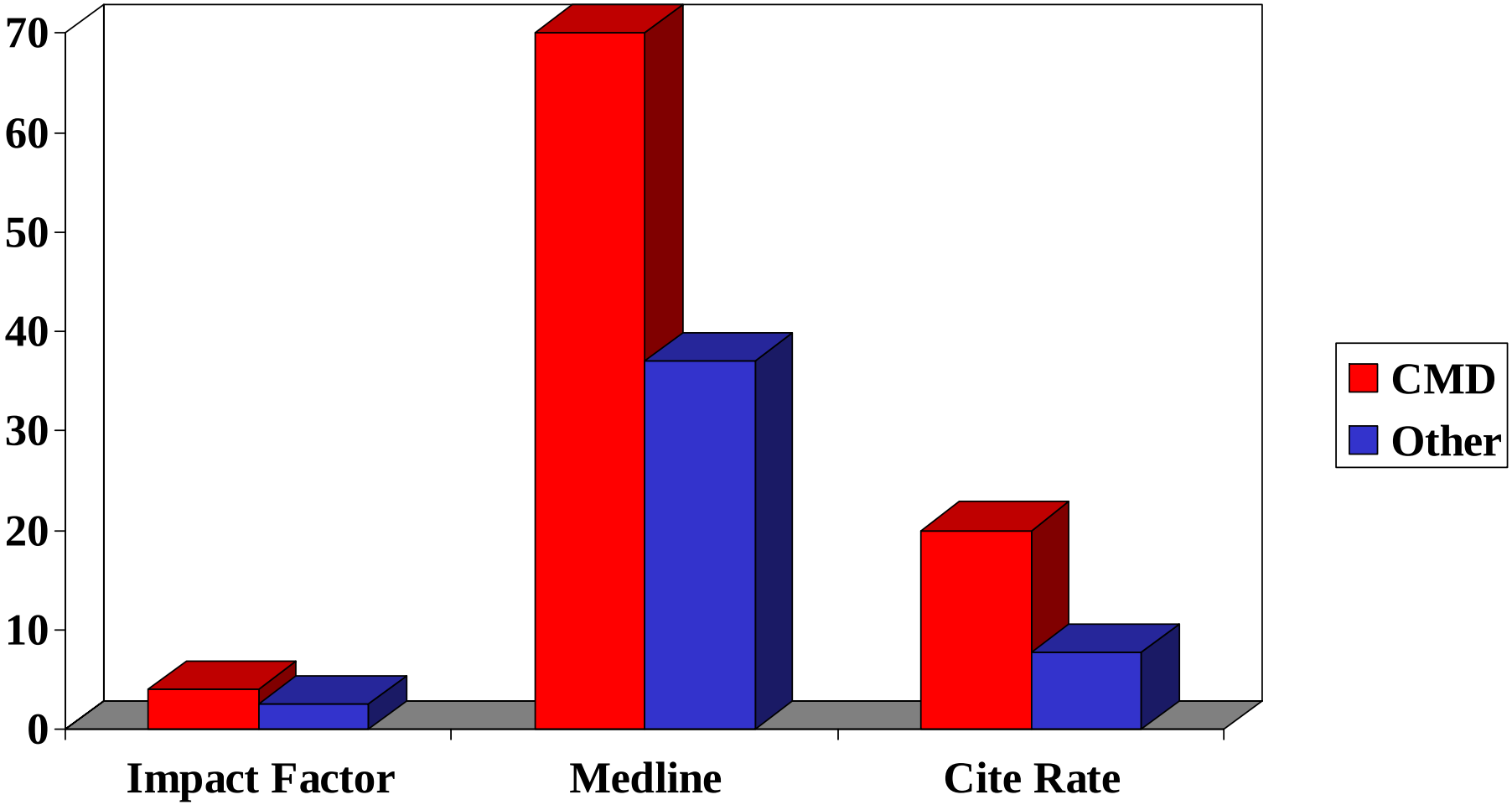
CMD writes up studies, review articles, abstracts, journal supplements, product monographs, expert commentaries and textbook chapters. It conducts meta-analyses, & organizes journal supplements, satellite symposia, and consensus conferences as well as advisory boards for its clients

[CMD] “strives to exceed the expectations of our clients and to assist them in achieving their strategic objectives”.

ANXIETY
POST-TRAUMATIC STRESS DISORDER

Author—Title	Vendor	Status
Author TBD—(640) Sertraline vs. placebo in PTSD	Paladin	Poster presented at ECNP, 1997. Paper is completed, but revisions are needed.
Author TBD—(671) Title TBD	Paladin	Poster presented at ECNP, 1998. First draft completed, but additional analyses needed. Both 640 and 671 studies to be submitted soon. One will go to *New England Journal of Medicine* and the other to *JAMA*.

Analysis of CMD Articles



Healy & Cattell 2003, British J Psychiatry 183, 22-27

Subject: Study 334 Manuscript
Author: Ian W. Henry
Date: 16/10/95

… It is also important we publish this study soon given the imminence of the ZOLOFT launch in France …

Finally K could you please forward to me the list of French investigators identifying the proposed authors. I would like to give Pfizer France the chance to comment on these.

SUICIDAL ACTS IN ANTIPSYCHOTIC TRIALS

DRUG	PATIENT NO	SUICIDES	SUICIDAL ACTS
RISPERDAL	2607	9	43
Comparator	601	1	5
Placebo	195	0	1
ZYPREXA	2500	12	?
Comparator	810	1	?
Placebo	236	0 (1)	**?**
SEROQUEL	2523	1	4
Comparator	426	0	2
Placebo	206	0	0
SERTINDOLE	2194	5	20
Comparator	632	0	2
Placebo	290	0	1
GEODON	2993	6	??
Comparator	951	1	??
Placebo	424	0	??

Alderman et al 1998 – “sertraline is **safe** and likely to be **effective** in pediatric patients.” **(9%)**

Ambrosini, Wagner et al 1999 – “sertraline is **effective safe and well tolerated” (5.7%)**

Keller, Wagner et al 2001 – “study provide[s] evidence of the **safety & efficacy** of paroxetine in the treatment of adolescent depression **(5.4%)**

Wagner et al 2002 – “these results indicate that treatment of children and adolescents with paroxetine is **safe and generally well-tolerated**.

Geller, Wagner et al 2002 – “paroxetine is a **safe and effective** treatment for OCD in pediatric pts”

Wagner et al 2003 – “sertraline is an **effective and well tolerated** treatment for children and adolescents with MDD”

LIPPINCOTT WILLIAMS & WILKINS

Journal of the American Academy of
CHILD & ADOLESCENT PSYCHIATRY

Volume 40(7) July 2001 pp 762-772

Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial

[Articles]

KELLER, MARTIN B. M.D.; RYAN, NEAL D. M.D.; STROBER, MICHAEL PH.D.; KLEIN, RACHEL G. PH.D.; KUTCHER, STAN P. M.D.; BIRMAHER, BORIS M.D.; HAGINO, OWEN R. M.D.; KOPLEWICZ, HAROLD M.D.; CARLSON, GABRIELLE A. M.D.; CLARKE, GREGORY N. PH.D.; EMSLIE, GRAHAM J. M.D.; FEINBERG, DAVID M.D.; GELLER, BARBARA M.D.; KUSUMAKAR, VIVEK M.D.; PAPATHEODOROU, GEORGE M.D.; SACK, WILLIAM H. M.D.; SWEENEY, MICHAEL PH.D.; WAGNER, KAREN DINEEN M.D., PH.D.; WELLER, ELIZABETH B. M.D.; WINTERS, NANCY C. M.D.; OAKES, ROSEMARY M.S.; MCCAFFERTY, JAMES P. B.S.

October 1998

SEROXAT/PAXIL
ADOLESCENT DEPRESSION
Position piece on the phase III clinical studies

EXECUTIVE SUMMARY

Results from the 2 placebo-controlled, phase III clinical trials designed to assess the efficacy and safety of Seroxat/Paxil in adolescents with major depression are now available.

Study 329 (conducted in the US) showed trends in efficacy in favour of Seroxat/Paxil across all indices of depression. However, the study failed to demonstrate a statistically significant difference from placebo on the primary efficacy measures. The second study (study 377), which was conducted in Europe, South America, South Africa and the United Arab Emirates, showed a high placebo response rate and failed demonstrate any separation of Seroxat/Paxil from placebo.

Data from these 2 studies are insufficiently robust to support a label change and will therefore not be submitted to the regulatory authorities. Results from Study 329 will be presented in abstract form at the ECNP meeting (Paris, November 1999) and a full manuscript will be progressed. There are no plans to publish data from Study 377.

TARGET

To effectively manage the dissemination of these data in order to minimise any potential negative commercial impact.

i) regulatory agencies would not approve a statement indicating that there are no safety issues in adolescents, as this could be seen as promoting off-label use

ii) it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.

- Positive data from Study 329 will be published in abstract form at the ECNP (Paris, November 1998) and a full manuscript of the 329 data will be progressed.

Papers

Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial

ELPS

This is an abridged version; the full version is on bmj.com

Leif Bjermer, Hans Bisgaard, Jean Bousquet, Leonardo M Fabbri, Andrew P Greening, Tari Haahtela, Stephen T Holgate, Cesar Picado, Joris Menten, S Balachandra Dass, Jonathan A Leff, Peter G Polos

Abstract

Objectives To assess the effect of montelukast versus salmeterol added to inhaled fluticasone propionate on asthma exacerbation in patients whose symptoms are inadequately controlled with fluticasone alone.
Design and setting A 52 week, two period, double blind, multicentre trial during which patients whose symptoms remained uncontrolled by inhaled corticosteroids were randomised to add montelukast or salmeterol.
Participants Patients (15-72 years; n = 1490) had a clinical history of chronic asthma for ≥ 1 year, a baseline forced expiratory volume in one second (FEV$_1$) value 50-90% predicted, and a β agonist improvement of ≥ 12% in FEV$_1$.
Main outcome measures The primary end point was the percentage of patients with at least one asthma exacerbation.
Results 20.1% of the patients in the group receiving montelukast and fluticasone had an asthma exacerbation compared with 19.1% in the group receiving salmeterol and fluticasone; the difference was 1% (95% confidence interval −3.1% to 5.0%). With a risk ratio (montelukast-fluticasone/salmeterol-fluticasone) of 1.05 (0.86 to 1.29), treatment with montelukast and fluticasone was shown to be non-inferior to treatment with salmeterol and fluticasone. Salmeterol and fluticasone significantly increased FEV$_1$ before a β agonist was used and morning peak expiratory flow compared with montelukast and fluticasone ($P \leq 0.001$), whereas FEV$_1$ after a β agonist was used and improvements in asthma specific quality of life and nocturnal awakenings were similar between the groups. Montelukast and fluticasone significantly ($P = 0.011$) reduced peripheral blood eosinophil counts compared with salmeterol and fluticasone. Both treatments were generally well tolerated.
Conclusion The addition of montelukast in patients whose symptoms remain uncontrolled by inhaled fluticasone could provide equivalent clinical control to salmeterol.

Introduction

Current guidelines recommend inhaled corticosteroids as first line treatments for patients with persistent asthma.[1,2] However, many patients remain symptomatic despite this treatment, and inflammation of the airways may persist with inhaled and even oral corticosteroids.[3] Combination treatment, adding an inhaled long acting β agonist to an inhaled corticosteroid, is therefore recommended in current guidelines to achieve additional control.[1,2] An alternative approach is to add a leukotriene receptor antagonist to an inhaled corticosteroid.[4] Cysteinyl leukotrienes released by eosinophils and mast cells mediate pro-inflammatory events in asthma.[5] Montelukast is a leukotriene receptor antagonist that improves asthmatic inflammation and prevents bronchoconstriction.[6-8] Few data are available, however, to compare these alternative strategies.

We report a randomised controlled trial of adding salmeterol or montelukast to an inhaled corticosteroid for patients who remained symptomatic while using an inhaled corticosteroid alone, which assessed the rate of asthma exacerbations over a one year period.

Methods

Study design and patients

This study was a randomised, double blind, double dummy, parallel group, multicentre study of 52 weeks including a four week run-in period when patients received non-blinded inhaled dry powder fluticasone 100 μg twice daily. During the last two weeks of this period, single blind placebo salmeterol (metered dose inhaler) and placebo montelukast were added. A 48 week period of double blind, double dummy treatment followed, during which in addition to fluticasone 100 μg twice daily, patients received either montelukast 10 mg once daily (in the evening) or salmeterol 50 μg twice daily. The study was conducted between January 2000 and December 2001.

Patients were aged 15-72 years and had a history of chronic asthma for one year or longer, a baseline forced expiratory volume in one second (FEV$_1$) of 50-90% predicted, and an improvement of 12% or

Department of Respiratory Medicine and Allergology, University Hospital, SE-221 85 Lund, Sweden
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Leonardo M Fabbri *professor*

continued over

BMJ 2003;327:891–5

P+

The full list of investigators appears on bmj.com

Alderman et al 1998 – “sertraline is **safe** and likely to be **effective** in pediatric patients.” **(9%)**

Ambrosini, Wagner et al 1999 – “sertraline is **effective safe and well tolerated” (5.7%)**

Keller, Wagner et al 2001 – “study provide[s] evidence of the **safety & efficacy** of paroxetine in the treatment of adolescent depression **(5.4%)**

Wagner et al 2002 – “these results indicate that treatment of children and adolescents with paroxetine is **safe and generally well-tolerated**.

Geller, Wagner et al 2002 – “paroxetine is a **safe and effective** treatment for OCD in pediatric pts”

Wagner et al 2003 – “sertraline is an **effective and well tolerated** treatment for children and adolescents with MDD”

American College of Neuropsychopharmacology

EXECUTIVE SUMMARY

PRELIMINARY REPORT OF THE TASK FORCE ON
SSRIs AND SUICIDAL BEHAVIOR IN YOUTH

January 21, 2004

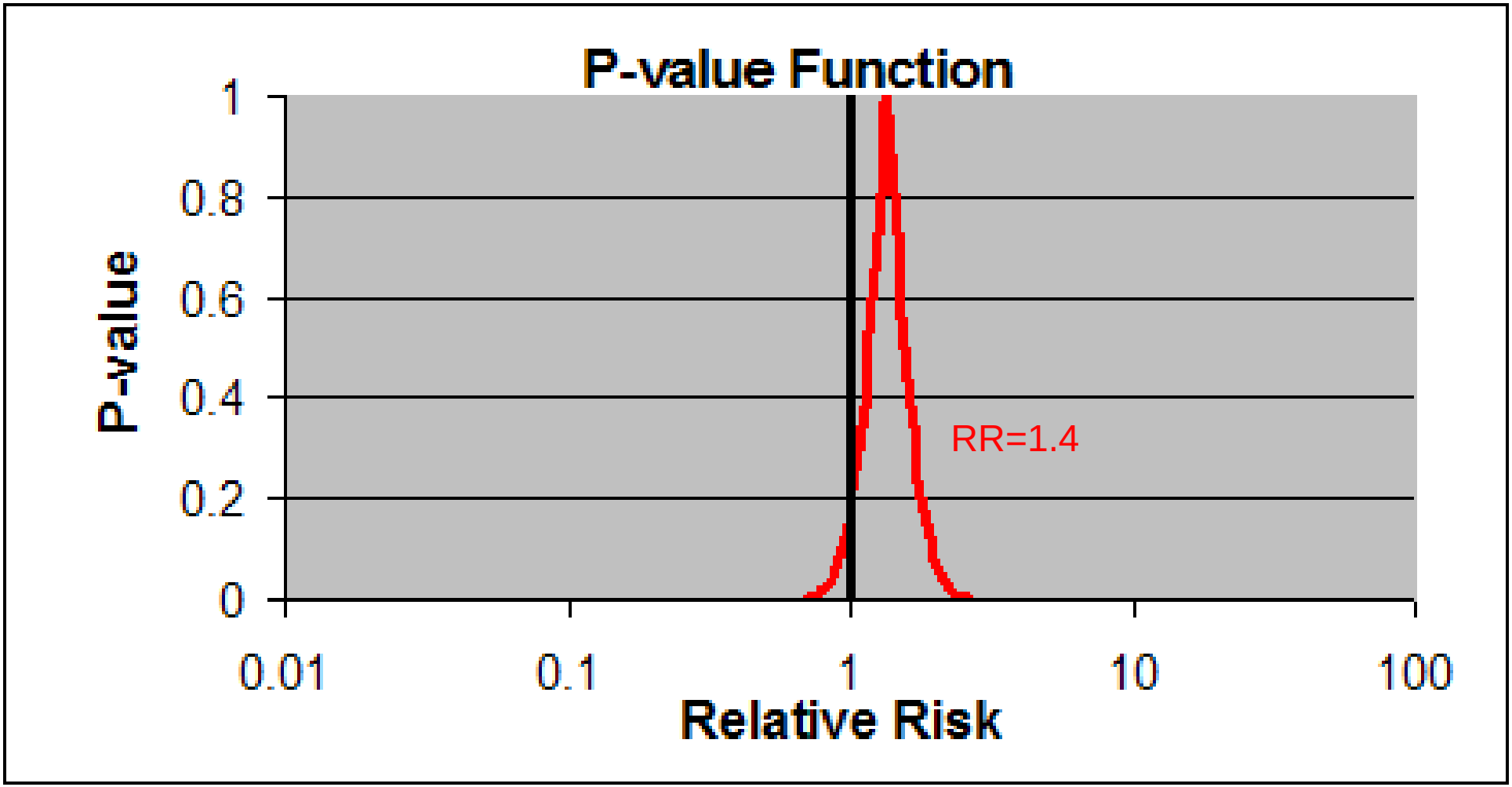
"The Task Force concluded that taking SSRIs or other new generation antidepressant drugs does not increase the risk of suicidal thinking or suicide attempts."

First, clinical trials of more than 2,000 youth found that there were no statistically significant increases in suicidal behavior and suicidal thinking. Most strikingly, there were no suicide deaths in any of the trials. Further, clinical trials of more than 20,000 adults also find that

SSRIs are not linked to suicide. Although no convincing evidence supports a link, the Task Force plans to conduct further analyses in the forthcoming final version of its report.

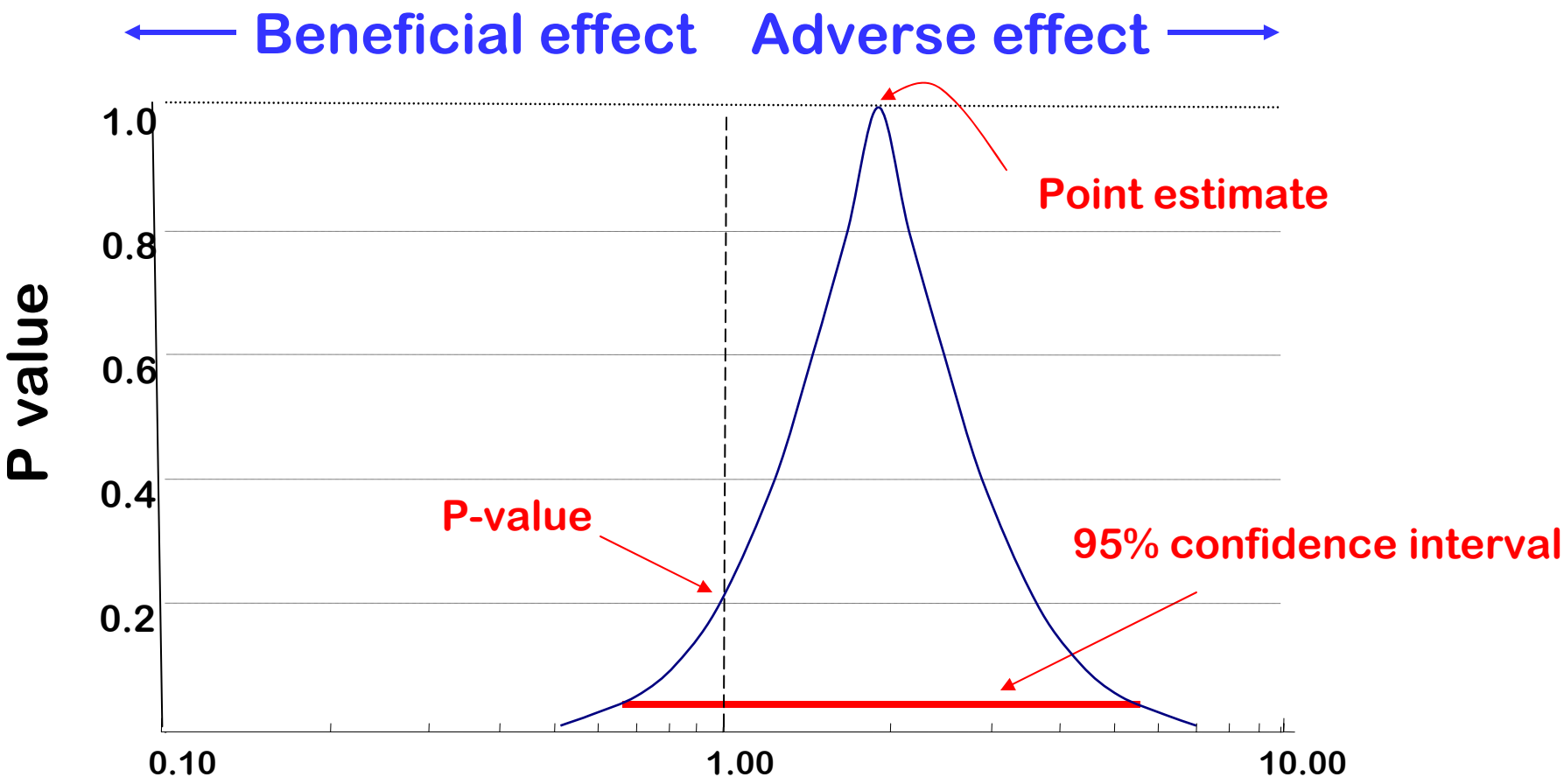
The evidence from case reports linking SSRIs to suicidal behavior is weak. The most likely explanation for cases of suicide or attempted suicide while taking SSRIs is that the underlying depression is responsible, not the SSRIs.

American College of Neuropsychopharmacology

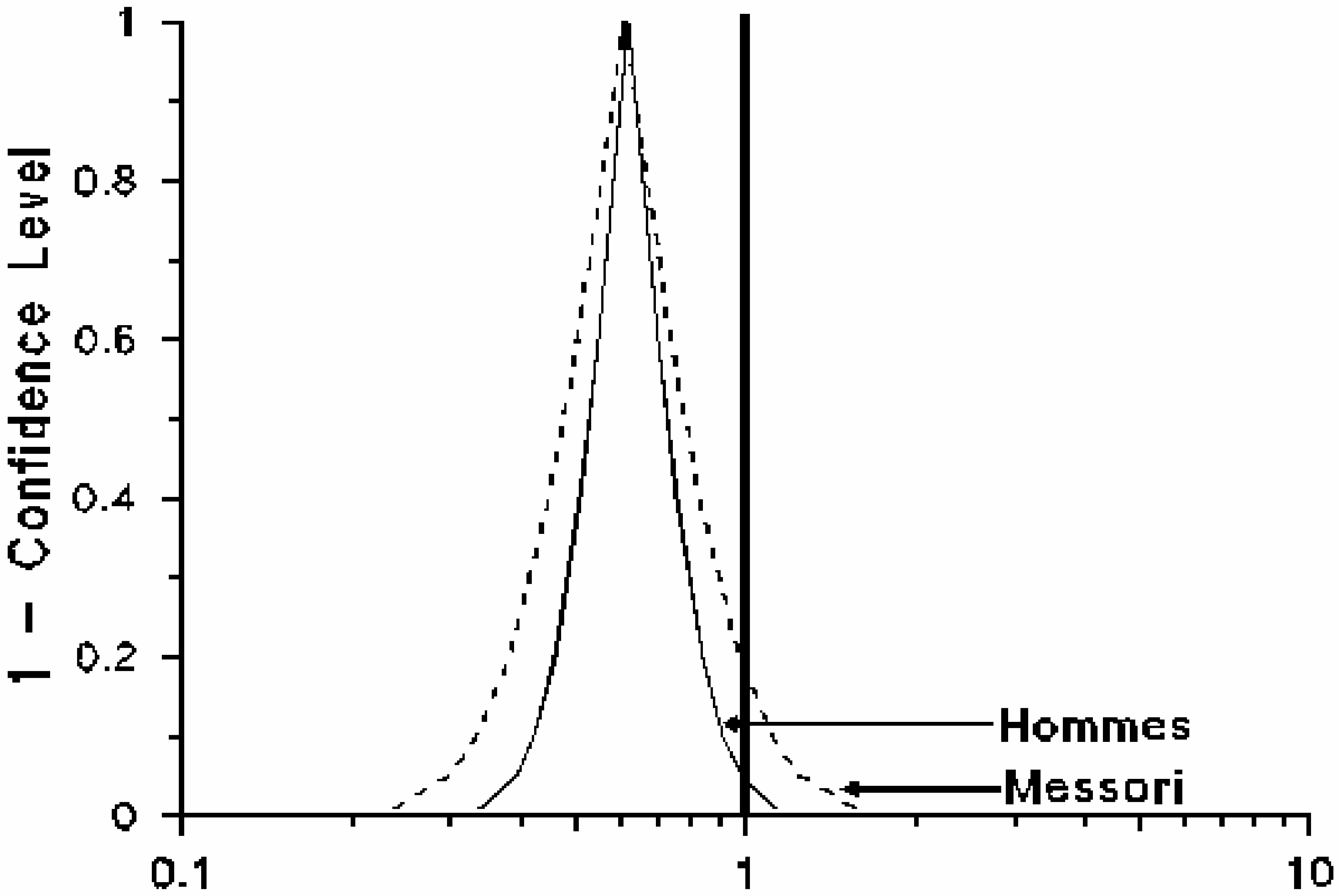


January 21, 2004

P-Value Function



HOMMES v MESSORI



The paper by Hommes et al reports a meta-analysis of 6 RCTs comparing subcutaneous heparin with continuous I/V heparin for the treatment of DVT.

The result of our calculation was an odds ratio of 0.61 (95% CI, 0.298 to 1.251; P > 0.05); this figure differs greatly from the value reported by Hommes et al,odds ratio, 0.62 (95% CI, 0.39 to 0.98; P < 0.05)

Based on our recalculation of the overall odds ratio, we concluded that subcutaneous heparin is not more effective than intravenous heparin, **exactly the opposite to that of Hommes and colleagues.**…"

Messori et al, Ann Intern Med 1993,118, 77-78.

Critical Reviews in Psychiatry
Brown T, Wilkinson G
Gaskell 1998 p 177

(c) Statistical analysis

(i) What does a 95% confidence interval (CI) mean?

If a series of identical studies was carried out repeatedly on different samples from the same population and a 95% CI for the odds ratio calculated in each study, then, in the long run, 95% of these CIs would include the true population.

Alternatively, there is a one in 20 chance that a similar study carried out in a similar population would produce results within this range.

(ii) If a 95% CI of an odds ratio contains the number 1.0, what does this mean?

The odds ratio is not significant.

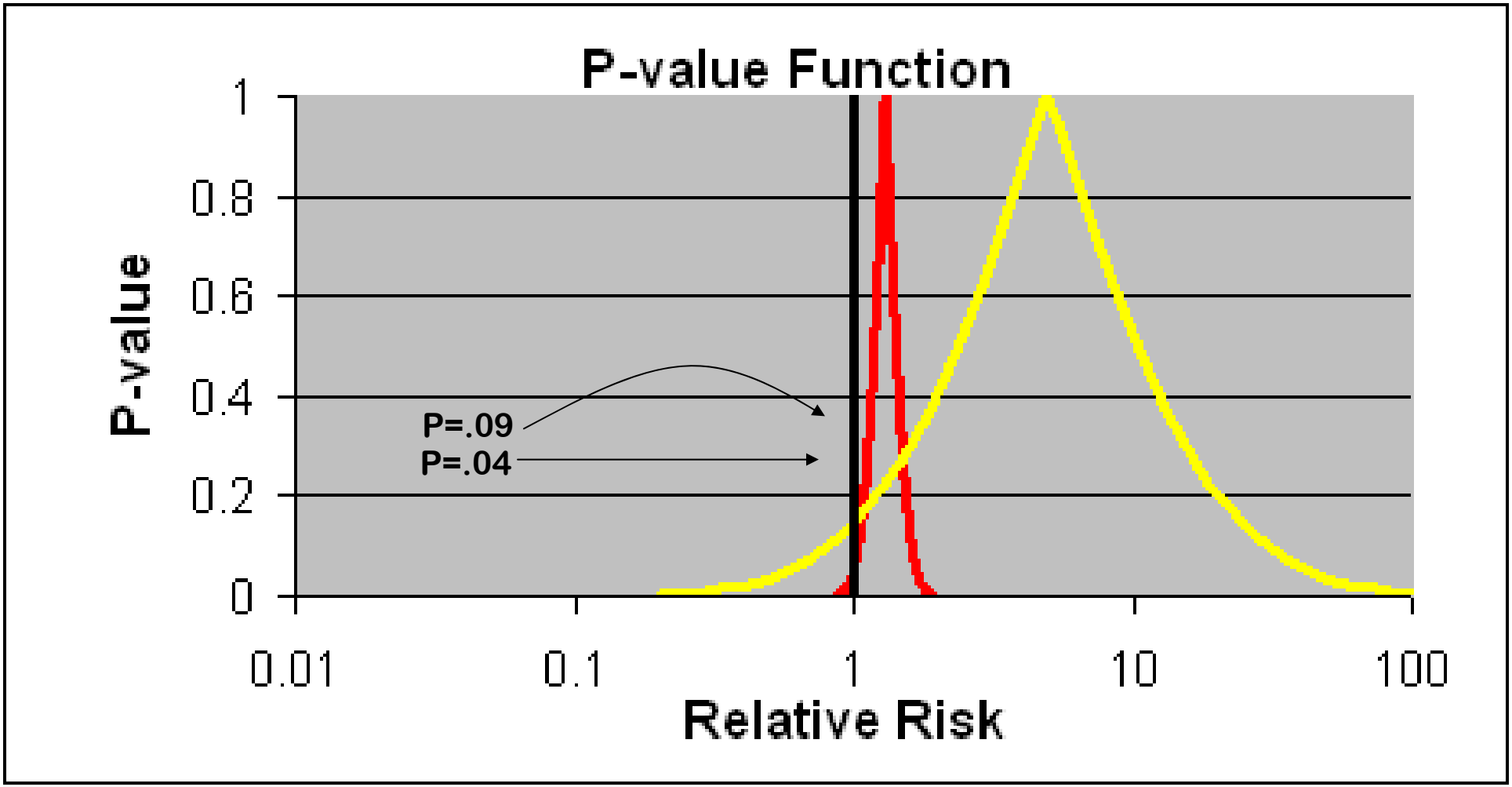
Would your decision about whether to use this intervention be the same at the upper confidence limit as at the lower confidence limit?

Critical Appraisal Skills Programme (CASP)

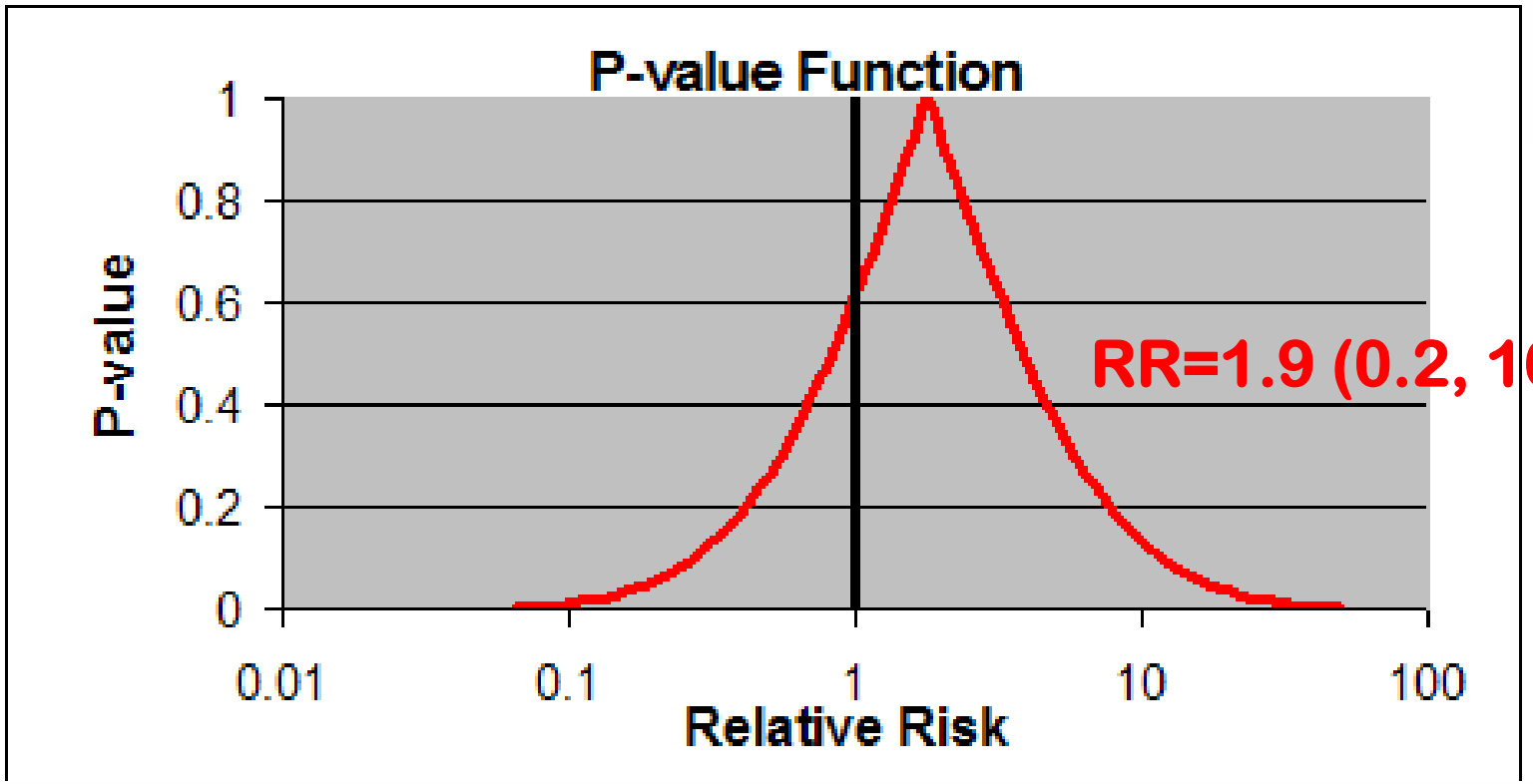
Oxman AD et al JAMA 1994 272, 1367-1371

What the data show

Drug A **Drug B**



Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression

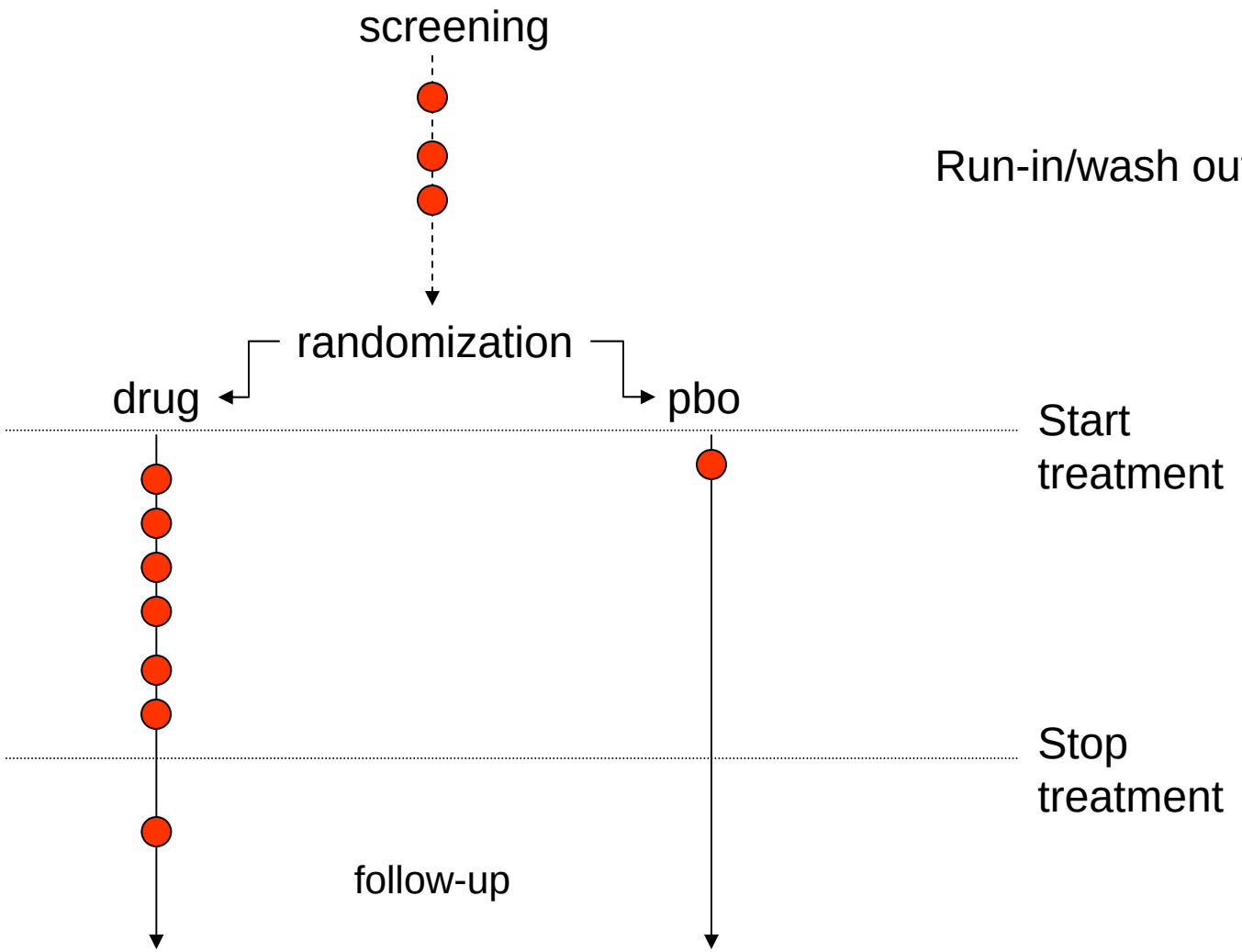


Conclusion—Data from these trials do not show that fluoxetine is associated with an increased risk of suicidal acts or emergence of substantial suicidal thoughts among depressed patients.

BMJ VOLUME 303 21 SEPTEMBER 1991

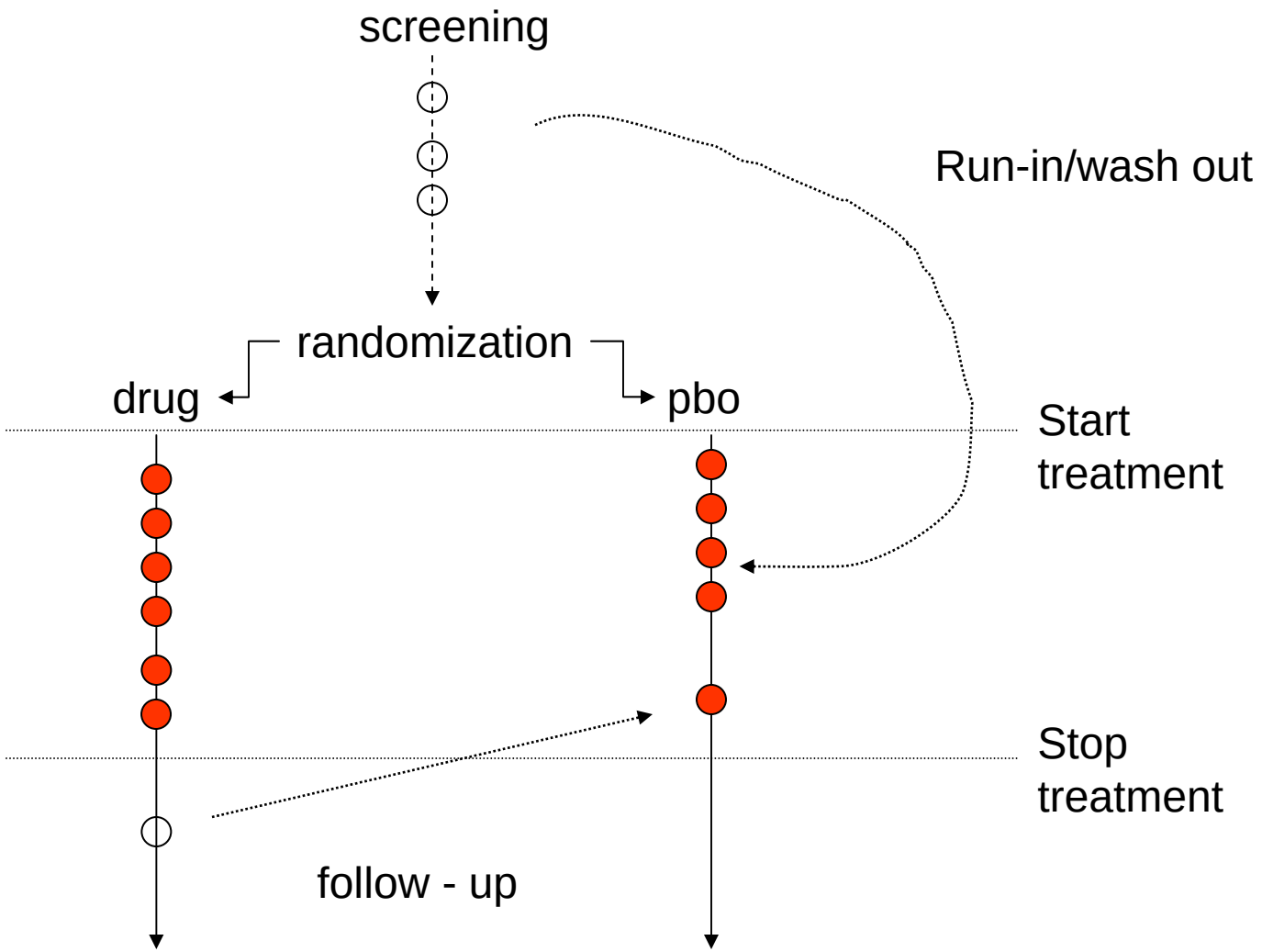
FLUOXETINE – PAROXETINE - SERTRALINE ADULT TRIALS

Occurrence of suicidal acts

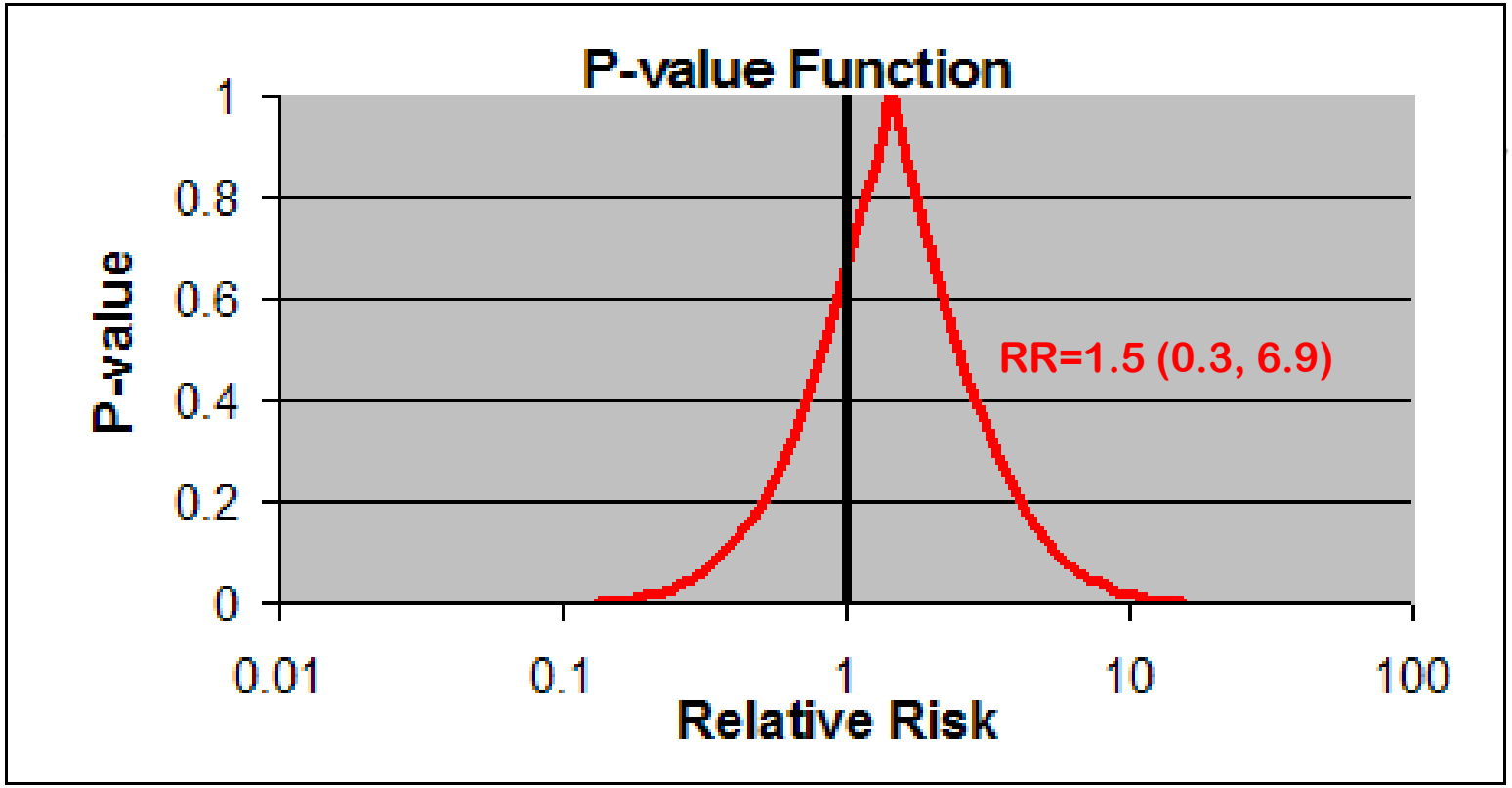


FLUOXETINE – PAROXETINE - SERTRALINE ADULT TRIALS

Reporting of suicidal acts

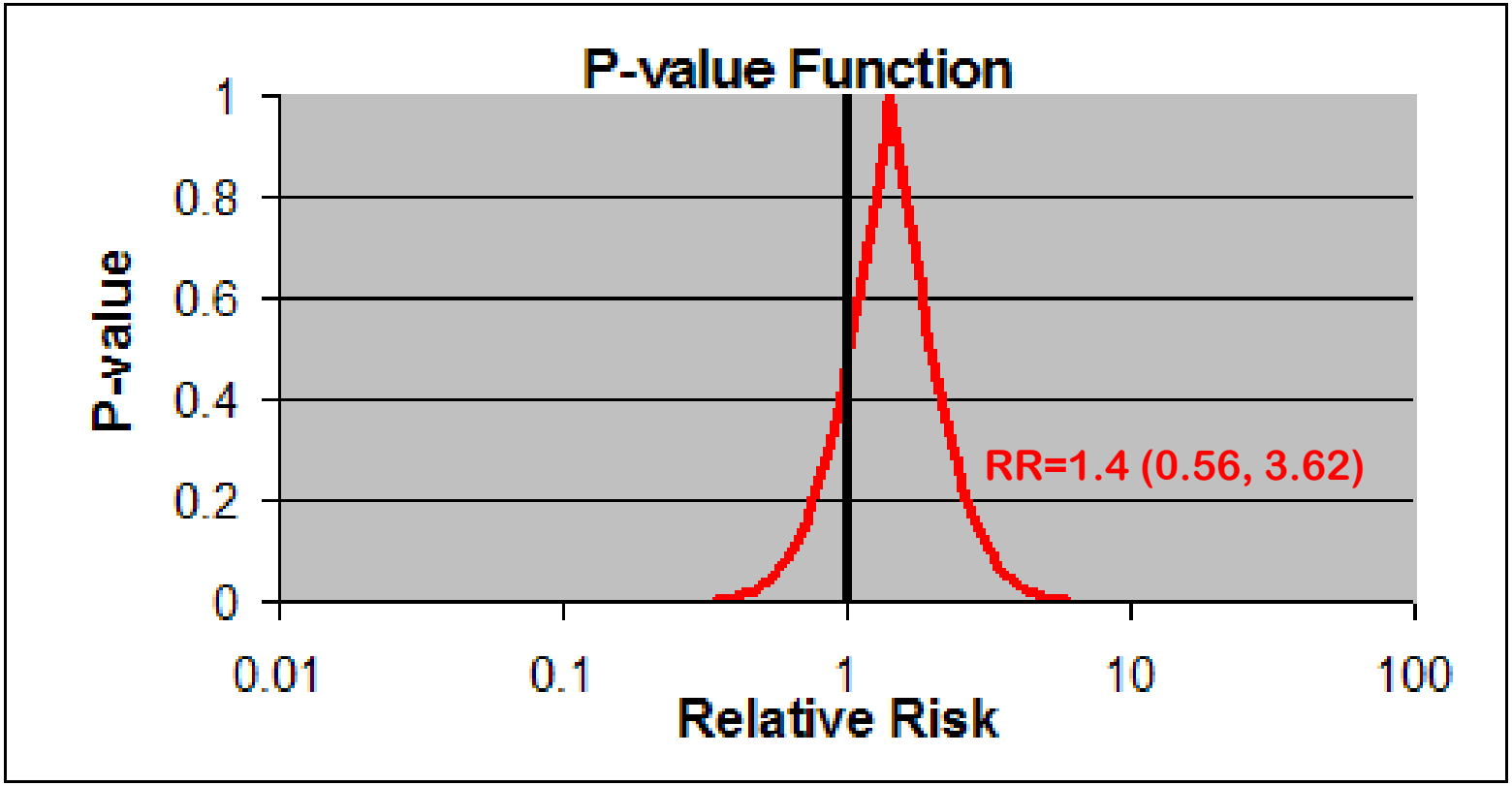


Lack of Association Between Fluoxetine and Suicidality in Bulimia Nervosa



"Analysis of the incidence of suicidal acts did not indicate an increased risk with patients with bulimia nervosa treated with fluoxetine compared to placebo"

Brief Report



"The only possible conclusion supported by the present data is that prescription of SSRI antidepressants is not associated with greater risk of completed suicide."

ELSEVIER

Journal of Affective Disorders 68 (2002) 183–190

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Research report

Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database

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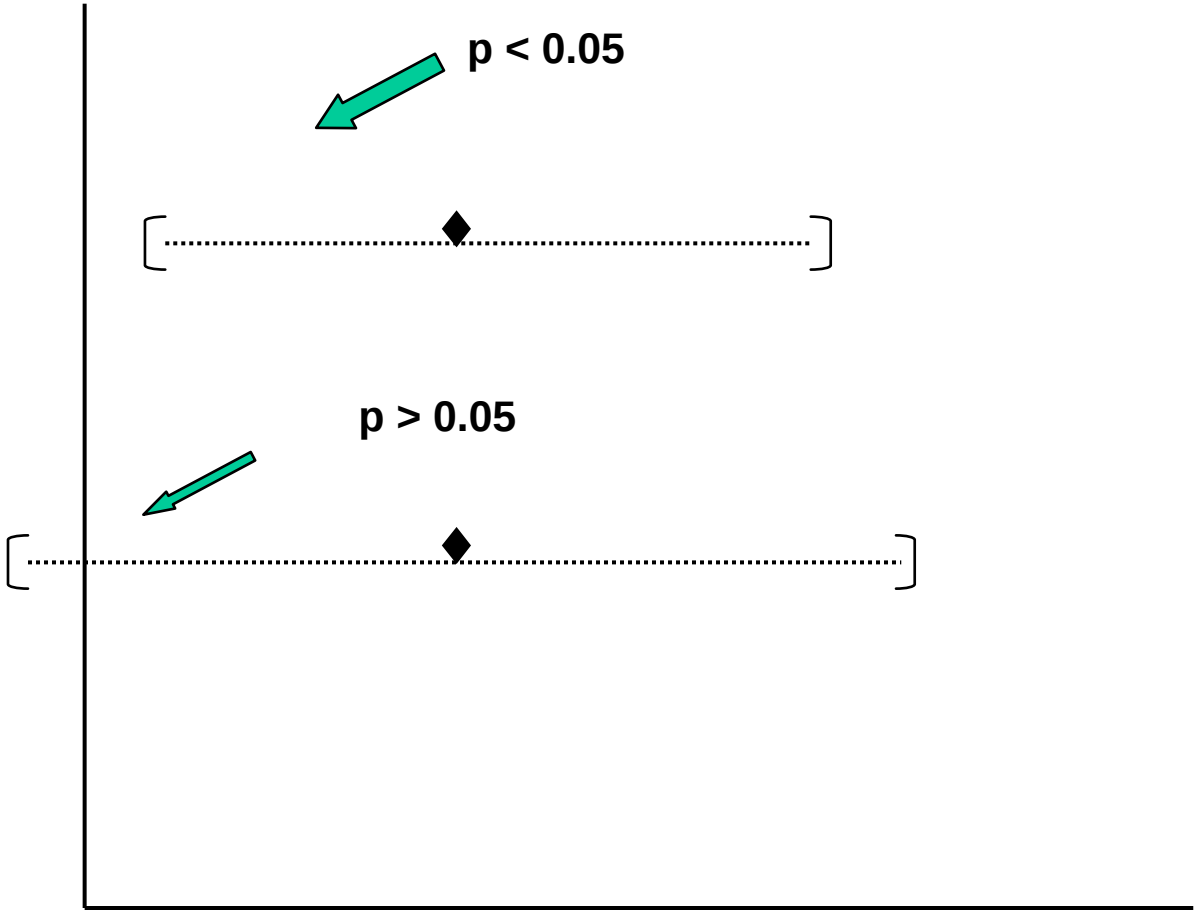
Received 26 December 2000; accepted 21 February 2001

"We found .. suicide risk among patients with anxiety disorders is higher than in the general population by a factor of 10 or more. Such a finding was unexpected….

11 Suicides in 12,914 on Drug
v 0 Suicides in 3875 on Placebo

WHAT DATA MEANS
FISHER v NEYMANN



FDA will send out this information which they concede is just early signal information .. it sounds good in principle. But I want you to think about it in terms of your reputation. It is really the reputation of a brand that is being signalled.

Imagine someone reporting that they had early information that you may be a child molester. I know that sounds extreme but it is that type of thing... It is just an allegation.. (but) that is what people will remember, and that is the reason there is a lot of concern about presenting early signal information when you don't really have any proof.

It is very different than the kind of rigorous process we had in the past, where you had to do a trial and it had to be statistically significant before you presented that".

Paul Anthony, PhARMA, June 2005

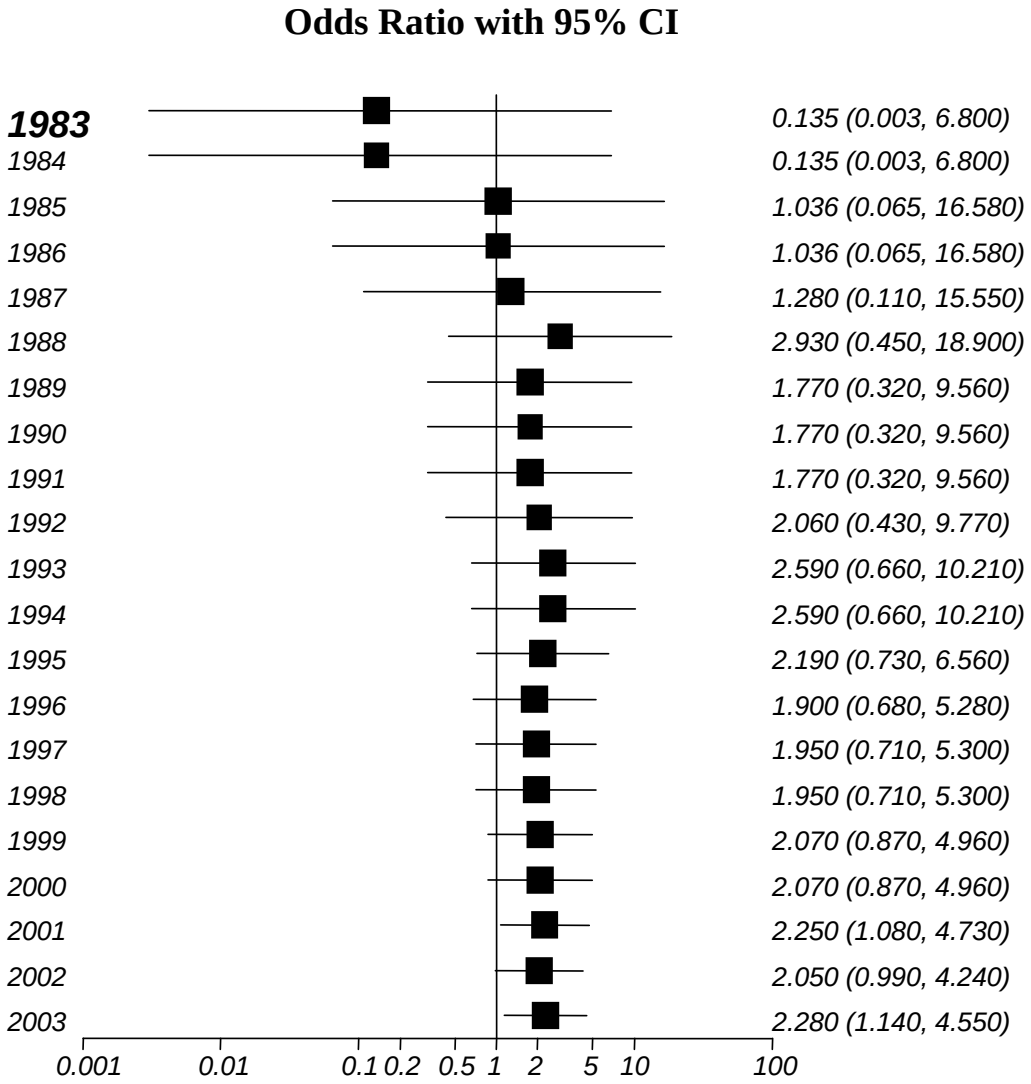
HOSTAGE TO POWER

Low power	**=**	**Problem not Real**
Prblm nt real	**=**	**Overestimate benefit**
Overestimate Benefit	**=**	**Overuse**
Overuse	**=**	**Unnecessary Death & Injury**

Imagine for a moment that you have a pistol with a barrel having 100 chambers. Now, randomly place 95 bullets in those chambers. The gun represents a drug and the bullets represent a serious safety problem.

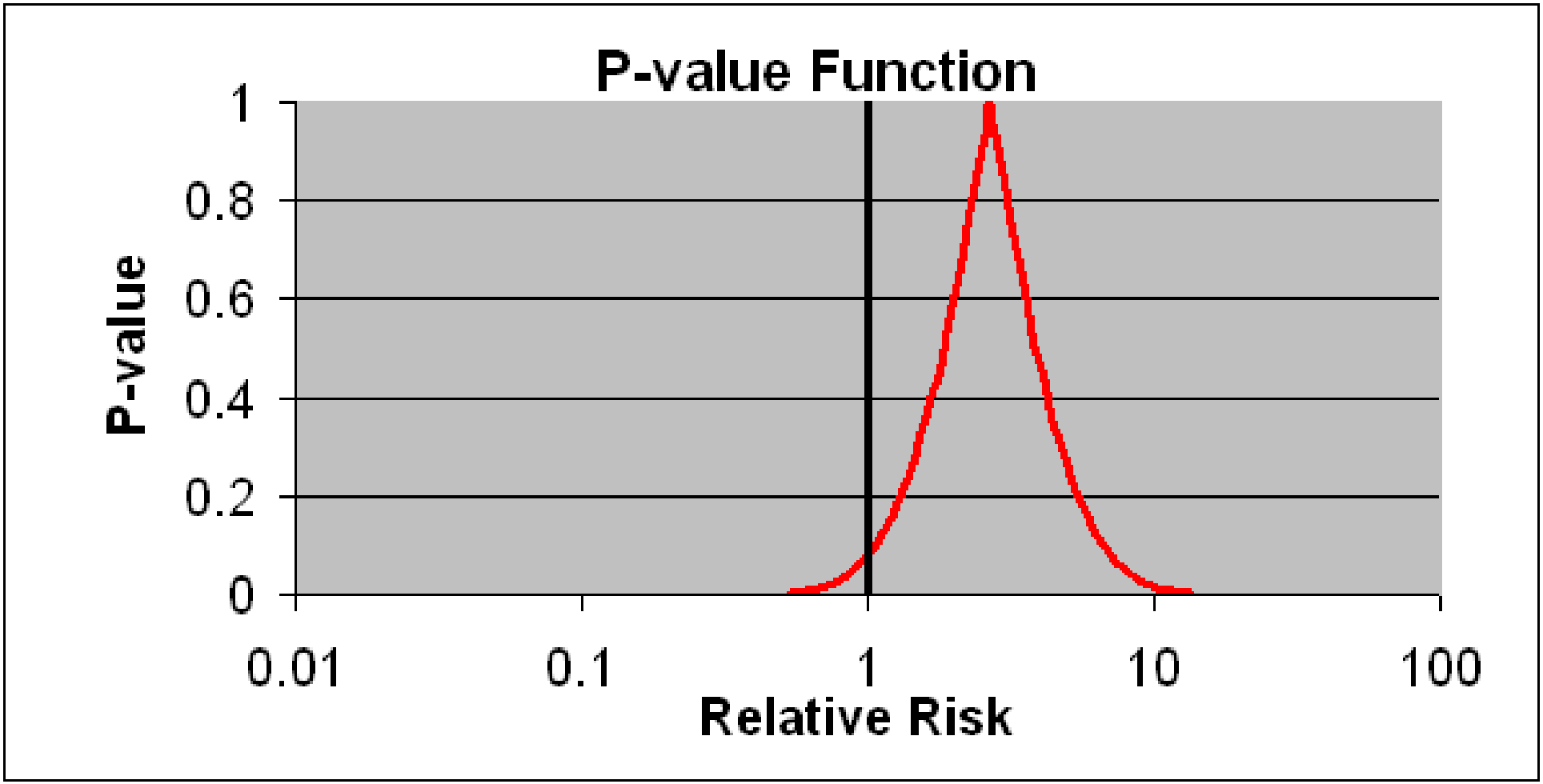
Using FDA's standard, only when you have 95 bullets or more in the gun will you agree that the gun is loaded and a safety problem exists.

David Graham Nov 18th 2004

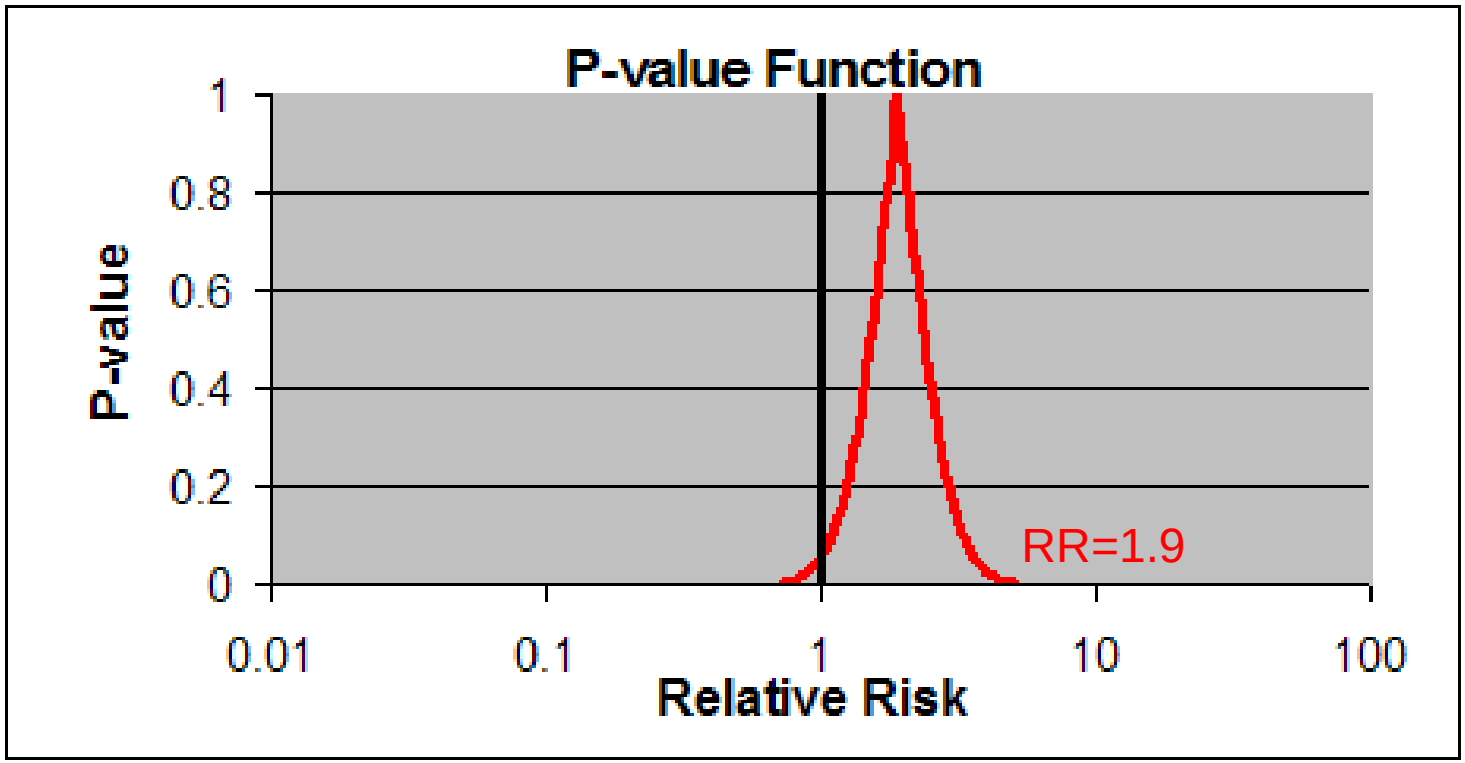

Odds Ratio with 95% CI
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
0.135 (0.003, 6.800)
0.135 (0.003, 6.800)
1.036 (0.065, 16.580)
1.036 (0.065, 16.580)
1.280 (0.110, 15.550)
2.930 (0.450, 18.900)
1.770 (0.320, 9.560)
1.770 (0.320, 9.560)
1.770 (0.320, 9.560)
2.060 (0.430, 9.770)
2.590 (0.660, 10.210)
2.590 (0.660, 10.210)
2.190 (0.730, 6.560)
1.900 (0.680, 5.280)
1.950 (0.710, 5.300)
1.950 (0.710, 5.300)
2.070 (0.870, 4.960)
2.070 (0.870, 4.960)
2.250 (1.080, 4.730)
2.050 (0.990, 4.240)
2.280 (1.140, 4.550)
0.001
0.01
0.1
0.2
0.5
1
2
5
10
100

EWG Placebo Controlled Suicides: RR = 2.66
95% C.I. 0.90, 7.90, p = 0.067

Sertraline, Fluvoxamine, Citalopram, Paroxetine, Escitalopram, Venlafaxine & Mirtazapine



Columbia/FDA meta-analysis of pediatric trials



"The data in aggregate indicate an increased risk of suicidality,in pediatric patients."

- Thomas Laughren, FDA, 2004.

ParentsMedGuide.org
helping parents help their kids

The Use of Medication in Treating Childhood and Adolescent Depression:
Information for Patients and Families

Prepared by the
American Psychiatric Association and
American Academy of Child and Adolescent Psychiatry
In consultation with
A National Coalition of Concerned Parents, Providers, and Professional Associations

Do antidepressants increase the risk of suicide?

There is no evidence that antidepressants increase the risk of suicide.

It does appear that these medications may affect the likelihood that a patient will actually tell someone about their suicidal thoughts or even a suicide attempt.

From my perspective as a child and adolescent psychiatrist this is actually a good thing, because it means you have the opportunity to intervene and keep the child safe.

David Fassler for APA and AACAP 2005

NEWS RELEASE

American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209

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lsward@psych.org

For Immediate Release:
October 15, 2004
Release No. 04-55

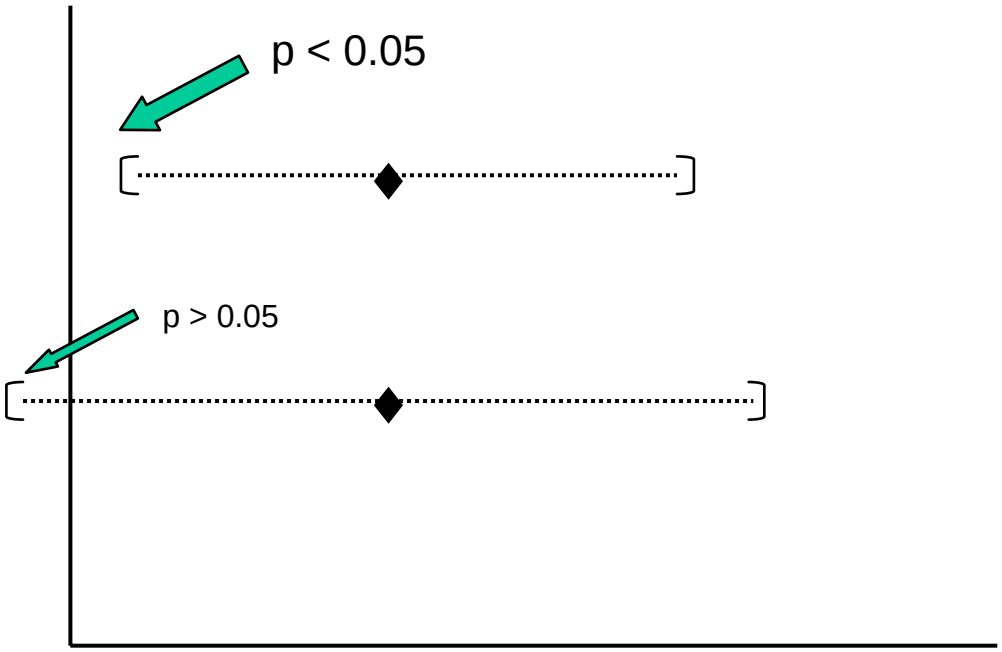
APA Responds to FDA's New Warning on Antidepressants

"The American Psychiatric Association believes that antidepressants save lives."

biggest threat to a depressed child's well-being is to receive no care at all.

We restate our continued deep concern that a "black box" warning on antidepressants may have a chilling effect on appropriate prescribing for patients. This would put seriously ill patients at grave risk. Recent prescription data suggest the current controversy over antidepressants has already lowered treatment rates; the new black box warning may further negatively impact treatment rates. The APA is working to help mitigate such an impact by collaborating with non-psychiatric physicians – including pediatricians and general practitioners – to help them better understand their patients' needs and properly diagnose, treat and monitor patients. Additionally, we hope the FDA will set in place a system to track the impact of the black box warning on prescribing patterns. This system should also track any increase in actions by patients to harm themselves as a result of reduced access to medically necessary treatment with antidepressants.

EFFICACY FOCUS



No effect

RR = 1

Risk difference (%) = 0

Positive effect

RR > 1.0

Risk difference > 0

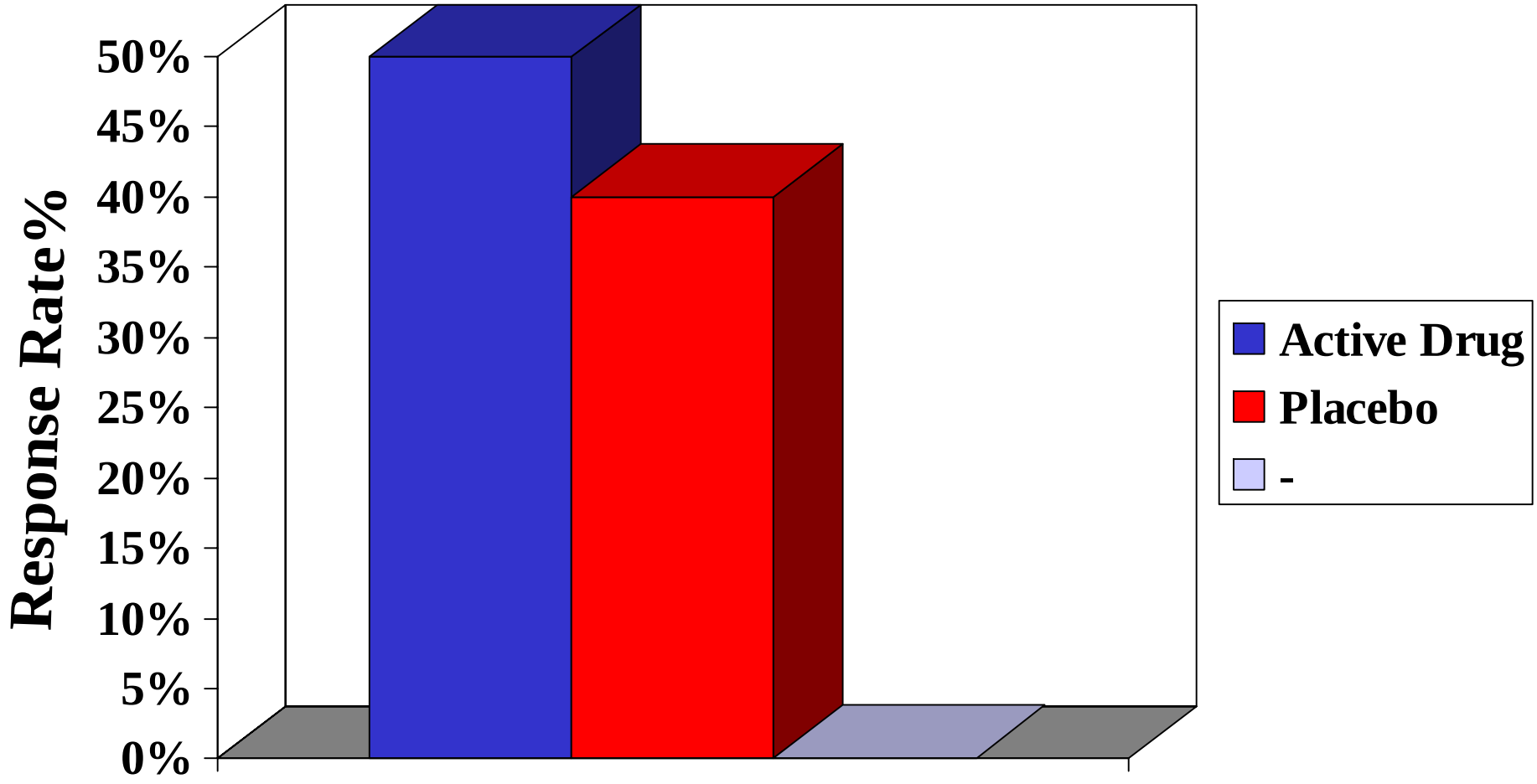
How do we interpret... two positive results in the context of several more studies that fail to demonstrate that effect?

I am not sure I have an answer to that but I am not sure that the law requires me to have an answer to that—fortunately or unfortunately.

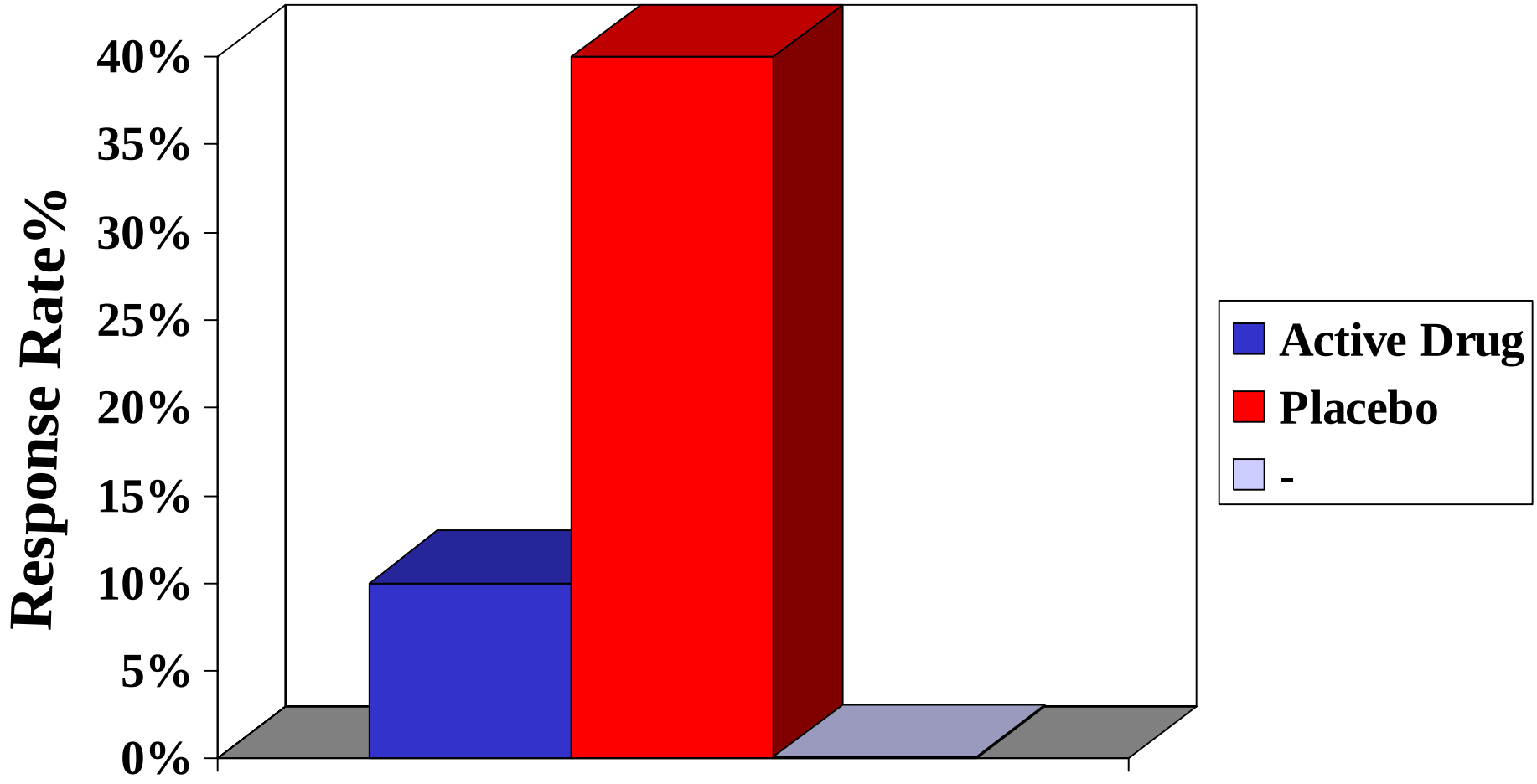
That would mean, in a sense, that the sponsor could just do studies until the cows come home until he gets two of them that are statistically significant by chance alone, walks them out and says he has met the criteria.

Paul Leber, Sertraline Approval Hearings 1991

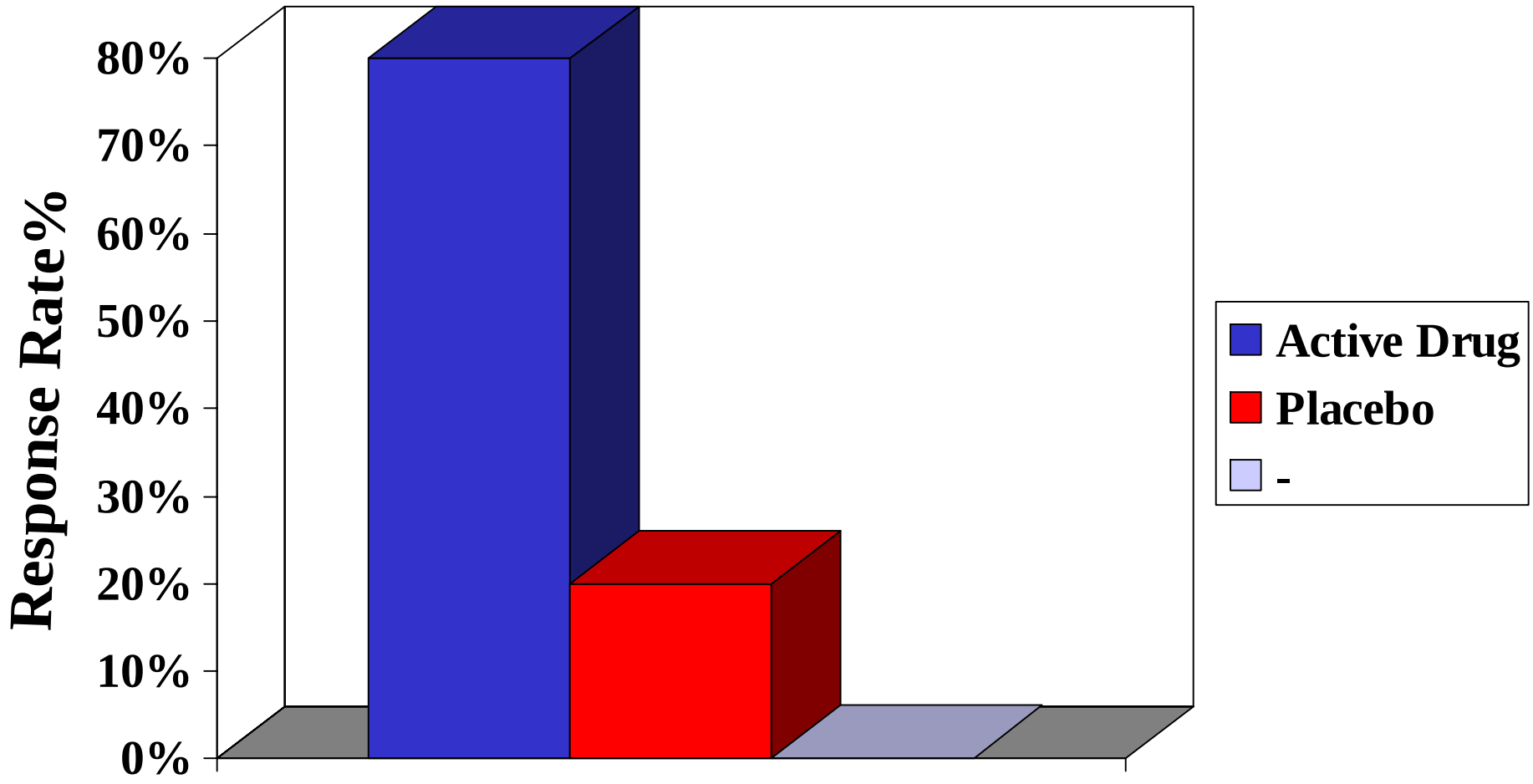
Drug v Placebo



Drug v Placebo



Drug v Placebo



For security against robbers
who snatch purses,
rifle luggage and crack safes,
one must fasten property with ropes
lock it up with locks,
bolt it with bolts.
This – for property owners – is
elementary good sense.

But when a strong thief comes along
he picks up the whole lot,
puts it on his back,
and goes on his way
with only one fear –
that ropes, and locks and bolts
may give way

Chuang Tzu 323 B.C.