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Dan J. Stein, Bernard Lerer and Stephen Stahl  
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## Evidence-based Psychopharmacology

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This book summarizes the recent advances in evidence-based pharmacological treatment of psychiatric disorders. There have been some significant developments in our understanding of the methods for systematically reviewing the literature, assessing clinical trials, and optimizing decision-making. This volume examines these issues with reference to the major psychiatric conditions and addresses issues such as selecting the best first-line psychopharmacological intervention for a particular disorder, for how long a particular intervention should be continued, and identifying the next-best treatment strategy should the first agent fail. The conditions covered include, amongst others, depression, schizophrenia, panic, posttraumatic stress disorder, obsessive-compulsive disorder, attention-deficit hyperactivity disorder, and eating disorders. There is also a chapter on the potential for complications as a result of adverse interactions between drugs. These issues lie at the heart of clinical psychopharmacology and the book will therefore appeal to all practicing clinicians, whether in a primary care or a specialist mental health setting.

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Dan J. Stein

University of Cape Town, South Africa

Bernard Lerer

Hadassah-Hebrew Medical Center, Israel

Stephen Stahl

University of California San Diego, USA



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## Contributors

**Abraham Bakker, MD**

National Centre for Eating Disorders  
Robert Fleury Stichting  
Leidschendam  
The Netherlands

**David S. Baldwin, MD**

Department of Psychiatry  
University of Southampton  
Southampton  
UK

**Joseph Biederman, MD**

Massachusetts General Hospital and  
Harvard University  
Boston MA  
USA

**Jacqueline Birks**

Cochrane Dementia and Cognitive  
Improvement Group  
University of Oxford  
Oxford  
UK

**Carlos Blanco, MD**

Department of Psychiatry  
Columbia College of Physicians  
and Surgeons  
New York NY  
USA

**C. Lindsay DeVane, PharmD**

Department of Psychiatry and Behavioral  
Sciences  
Medical University of South Carolina  
Charleston SC  
USA

**Robin Emsley, MB ChB, MMed, PhD**

Department of Psychiatry  
University of Stellenbosch  
Stellenbosch  
South Africa

**John Grimley Evans**

Cochrane Dementia and Cognitive  
Impairment Group  
University of Oxford  
Oxford  
UK

**Naomi A. Fineberg, MA, MBBS, MRCPsych**

Queen Elizabeth II Hospital  
Welwyn Garden City  
Herts  
UK

**Martine F. Flament, MD, PhD**

University of Ottawa Institute of Mental  
Health Resource  
Royal Ottawa Hospital  
Ottawa ON  
Canada

**viii**      **Contributors**

**Claudia Furino, BA**

University of Ottawa Institute of Mental  
Health Resource  
Royal Ottawa Hospital  
Ottawa ON  
Canada

**Tim M. Gale, PhD**

Department of Psychology  
University of Hertfordshire  
Hatfield  
Herts  
UK

**S. Nassir Ghaemi, MD**

Cambridge Hospital and Harvard University  
Cambridge MA  
USA

**Nathalie Godart, MD, PhD**

Department of Psychiatry  
Institut Mutualiste Montsouris  
Paris  
France

**Douglas J. Hsu, BS**

Cambridge Hospital and Harvard University  
Cambridge MA  
USA

**Jeffrey Huffman, MD**

Massachusetts General Hospital  
and Harvard University  
Boston MA  
USA

**Michael R. Liebowitz, MD**

Department of Psychiatry  
Columbia College of Physicians and  
Surgeons  
New York NY  
USA

**Andrew A. Nierenberg, MD**

Massachusetts General Hospital  
and Harvard University  
Boston MA  
USA

**Piet Oosthuizen, MB ChB, MMed, PhD**

Department of Psychiatry  
University of Stellenbosch  
Stellenbosch  
South Africa

**Michael J. Ostacher, MD, MPH**

Massachusetts General Hospital  
and Harvard University  
Boston MA  
USA

**Roy Perlis, MD**

Massachusetts General Hospital  
and Harvard University  
Boston MA  
USA

**Claire Polkinghorn, MD**

Department of Psychiatry  
Royal South Hants Hospital  
Southampton  
UK

**C. Barbara Portier, MD**

Department of Psychiatry  
Sint Lucas Andreas Hospital  
Amsterdam  
The Netherlands

**Muhammad S. Raza, MD**

Department of Psychiatry  
Columbia College of Physicians and  
Surgeons  
New York NY  
USA

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**ix**      **Contributors**

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**Franklin R. Schneier, MD**

Department of Psychiatry  
Columbia College of Physicians  
and Surgeons  
New York NY  
USA

**Thomas Spencer, MD**

Massachusetts General Hospital  
and Harvard University  
Boston MA 02114  
USA

**Dan J. Stein, MD**

Department of Psychiatry  
University of Cape Town  
Cape Town  
South Africa

**Anton J. L. M. van Balkom, MD**

Department of Psychiatry  
Vrije Universiteit  
Amsterdam  
The Netherlands

**Gordon Wilcock**

Department of Care of the Elderly  
University of Bristol  
Bristol  
UK

**Timothy Wilens, MD**

Massachusetts General  
Hospital and Harvard University  
Boston MA  
USA



## Preface

The pioneers of modern psychopharmacology prided themselves on the empirical nature of their work, and the rigor of their clinical data. Evidence-based medicine emphasizes the importance of searching for relevant studies and making decisions in the light of the data (Sackett *et al.*, 1996), and therefore has immediate appeal for psychopharmacology. This volume attempts to summarize recent advances in the evidence-based medication treatment of psychiatric disorders.

Clinical decisions are only as good as the existing evidence, and critics have rightly pointed out the necessity for good clinical judgment and for further research when the data are poor (Klein, 1993; Wells, 1999; Rush, 2001). Nevertheless, there has been a steady growth in methods for systematically reviewing the literature, assessing the clinical trials database, and optimizing clinical decision-making (Chalmers and Altman, 1995; Eddy, 1996; Fawcett *et al.*, 1999). We therefore felt that it was timely to publish a collection of evidence-based articles in psychopharmacology.

This volume comprises articles on each of the major psychiatric disorders, and addresses questions such as: (1) what is the best first-line psychopharmacological intervention for a particular disorder? (2) how long should such an intervention be continued? and (3) what is the next best strategy should the first-line psychopharmacological agent fail? These questions lie at the heart of clinical psychopharmacology, and we are hopeful that the volume will therefore appeal to practicing clinicians, whether they work in a primary or specialty setting.

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## Introduction

Dan J. Stein

University of Cape Town, South Africa

This volume is based on the assumption that the concepts and methods of evidence-based medicine can make an important contribution to clinical psychopharmacology. In this introductory chapter, a brief background to evidence-based medicine is provided. The chapter outlines a definition of evidence-based medicine, considers some of the limitations of evidence-based medicine, discusses the growing emphasis on evidence-based guidelines and algorithms, and notes some of the evidence for evidence-based medicine.

### What is evidence-based medicine?

There has been a significant growth in attention to evidence-based medicine in the past two decades. A search of the internet database PubMed reveals two citations on evidence-based medicine in 1992, but 3037 in 2004. Articles on evidence-based psychiatry first began appearing in the mid-1990s, and have similarly demonstrated an exponential increase. An immediate question is whether evidence-based medicine is merely old wine in a new bottle, or whether it represents a novel conceptual approach, along with new methodologies.

Sackett, a seminal author in the emergence of this new focus, has written that evidence-based medicine is the “conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” (Sackett *et al.*, 1996). Evidence-based medicine addresses the question of how best to search the literature, how best to rate the quality of the relevant studies, and how best to synthesize the existing data (for example, using meta-analysis) (Guyatt and Rennie, 2002). Involvement of the patient in decision-making is also key.

The practice of evidence-based medicine involves, however, a good deal more than just the academic exercise of searching for and examining the existing research. In particular, evidence-based medicine involves “integrating individual clinical expertise with the best available external clinical evidence from systematic research” (Sackett *et al.*, 1996). Without clinical expertise, practice risks being tyrannized by

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evidence. Conversely, without current best evidence, practice risks becoming outdated (Cochrane, 1972). Thus, evidence-based medicine should not be equated with “cookbook” medicine.

An immediate objection to the prominence claimed by evidence-based medicine is that it has long been recommended that medicine be based on scientific principles, and that its interventions therefore lie on a solid empirical base (Flexner, 1910). Nevertheless, it should be remembered that randomized controlled trials (RCTs), the gold standard of evidence, are a relatively new development in medicine and psychiatry, as are the large electronic databases that provide ready access to such work. Certainly, RCTs are now so numerous that clinicians often do not read (Loke and Derry, 2003) or apply (Bruce *et al.*, 2003) them; appropriate theories and methods for synthesizing and applying the data at hand are therefore needed.

Even so, the limitations of the research base on which evidence-based medicine lies must be acknowledged. First, there may be few RCTs, or indeed, any studies, available to address any particular clinical question. The value of sequential and combined regimens is particularly difficult to address (Saver and Kalafut, 2001). Of course, absence of evidence of efficacy is not the same as absence of efficacy, so that while skepticism is crucial, it should also be tempered by clinical judgment. Similarly, a focus on measurable factors lies at the heart of evidence-based medicine, but in clinical psychopharmacology there are areas of practice where research measures are arguably insufficiently precise to match clinical phenomena (Williams and Garner, 2002). Certainly, despite the precedence given to RCTs, observational studies can provide accurate information (Concato *et al.*, 2000).

Second, even when RCTs exist, these may have significant limitations. The majority of the large controlled trials undertaken in psychopharmacology today are sponsored by the pharmaceutical industry, and aim to demonstrate to regulatory authorities the efficacy of medication over placebo. There are far fewer trials demonstrating the effectiveness of medication in the clinical context, where patient samples are much more heterogeneous than those who enter registration trials (Wells, 1999). Current clinical trials have other important limitations, including large numbers of subjects who respond to both medication and placebo (Parker *et al.*, 2003).

Third, meta-analysis of multiple available RCTs should be undertaken with due caution. Negative studies are often filed away in drawers rather than published, so that the published literature may be positively biased in favor of particular interventions (Melander *et al.*, 2003). Available studies may employ widely different methods, so that formal comparison is inappropriate. In an incisive criticism of a meta-analysis comparing pharmacotherapy and psychotherapy trials, for example, Klein (2000) argued that “Meta-analyses compared effect sizes from disparate studies that were not uniformly blind, random, controlled, or high quality.” Thus

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clinically useful distinctions can be obscured by using the supposed common metric of a single effect size.

Fourth, the conclusions of evidence-based medicine can be translated into inappropriately restricted policy. On the basis of the “evidence,” crucial variables affecting the operation of health systems may be overlooked (Birch, 1997), and there may be undue rationing of psychiatric medication and treatment. Interestingly, the use of untested non-conventional treatments may have increased after widespread introduction of evidence-based medicine into the UK (Williams and Garner, 2002). At the end of the day, if we are going to emphasize the importance of evidence, we will need to address the evidence for evidence-based medicine. We return to this question below.

## **Guidelines and algorithms**

Together with the growth of evidence-based medicine there has been the publication of a growing number of guidelines and algorithms, including those in the area of psychiatry and psychopharmacology. There is an increasing emphasis on “best practice” by clinicians, consumers, and health managers (in both public and private sectors); and guidelines are systematically developed statements designed to help practitioners and patients make decisions about appropriate health care for specific circumstances (Jackson and Feder, 1998), while algorithms attempt to clarify and present the inputs, sequences, and outputs involved in rule-based decision-making (Fawcett *et al.*, 1999).

Guidelines and algorithms are particularly useful insofar as they summarize the evidence (including data on efficacy, on effectiveness, and on cost-effectiveness), and point out areas where there are insufficient data and so where further research is needed (Patel *et al.*, 2001). They have the potential for helping to ensure that rigorous clinical standards are maintained, and for directing research to addressing gaps in the evidence base (Rush, 2001). Nevertheless, the proliferation of guidelines and algorithms does not necessarily translate into their being read, or into better clinical care, whether because of poor quality (Littlejohns *et al.*, 1999; Shaneyfelt *et al.*, 1999), or because of barriers to implementation (Cabana *et al.*, 1999).

A good guideline should: (1) identify the key decisions (e.g., diagnosis, assessment strategy, treatment choice); (2) review the relevant, valid evidence on the benefits, risks, and costs of alternative decisions; and (3) present recommendations in a concise, accessible, updated format (Woolf, 1992; Jackson and Feder, 1998). Guidelines should give an indication of the level of evidence used and consequent level of certainty of advice (there is a need to make decisions when there is no evidence). Guidelines must be time-stamped and regularly updated – evidence changes rapidly over time and updating may require multidisciplinary feedback.

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One area in which guidelines must show flexibility is in establishing a balance between specificity and generality (Klein, 1993). A useful guideline must walk a fine line between excessive specificity and excessive generality. Excessive specificity cannot be evidence-based, and by ignoring critical individual differences may be dangerous. Excessive generality, on the other hand, may provide insufficiently specific guidance for any particular decision.

Why don't physicians and consumers follow guidelines and algorithms (Haynes and Haines, 1998; Cabana *et al.*, 1999)? First, as noted above, the guidelines may be poor; they may not be user-friendly, relevant, or accurate. Second, there may be lack of effective dissemination and consequent poor access to recommendations. Third, there may be a lack of effective implementation and reinforcement. It may be crucial to target guidelines and algorithms in particular ways for particular users and purposes (Stein *et al.*, 2002).

Furthermore, important inherent limitations of guidelines and algorithms must be acknowledged. First, guidelines are only as good as the evidence base on which they rest; if this is poor, then the guideline may simply not provide an answer to any particular clinical question. Second, guidelines are no substitute for clinical expertise and judgment; they can't, for example, ensure an accurate diagnosis. The more complex the case, and the greater the specification of individual contributing clinical variables, arguably the less useful any particular guideline will be.

This volume is not specifically devoted to the development of guidelines and algorithms for clinical psychopharmacology. While guidelines are ideally evidence-based, many of those involved in the practice and teaching of evidence-based medicine focus rather on helping individual practitioners to address specific questions raised by patients. Here we focus on three key questions throughout: (1) What is the first-line pharmacotherapy? (2) For how long should this be maintained? and (3) What is the optimal approach to those who fail to respond to first-line pharmacotherapy?

**What is the evidence for evidence-based medicine?**

Given the emphasis of evidence-based medicine, an immediate question for those interested in its promulgation is whether there is any evidence that supports such a move. A small but growing literature has addressed this point, and the data are to some extent reassuring (Sackett *et al.*, 1996).

First, there are a number of positive controlled trials of teaching critical appraisal to medical students. Second, there is some evidence that educational outreach can modify health professional behavior, although not all data are consistent (Thomson-O'Brien *et al.*, 2000; Gilbody *et al.*, 2003). Third, there are a number of positive

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outcomes studies showing the benefit to patients of receiving effective therapies. Fourth, there are a number of positive controlled trials of the effects of guidelines and algorithms on clinical outcome, including work that has focused specifically on clinical psychopharmacology (Trivedi *et al.*, 2004).

On the other hand, although it has been argued that computerized decision support systems can promote adherence to guidelines and algorithms, RCTs have not demonstrated high rates of use or beneficial effects on the process or outcome of care (Rousseau *et al.*, 2003). Furthermore, there is some evidence that access to specialist services has been more beneficial than guideline implementations for the management of depression (Peveler & Kendrick, 2001). Thus, even while adhering to the principles of evidence-based medicine, there is a need for additional work to optimize evidence-based policy (Macintyre *et al.*, 2001).

While evidence-based medicine can be criticized for being insufficient, there are in reality few valid alternatives. We are continuously faced with the problem of dissociating researchers' therapy allegiances and their interpretation of treatment outcomes (Luborsky *et al.*, 2004). A tongue-in-cheek publication lists possible alternatives to evidence-based medicine as eminence-based medicine, vehemence-based medicine, eloquence-based medicine, providence-based medicine, diffidence-based medicine, nervousness-based medicine, and confidence-based medicine (Isaacs and Fitzgerald, 1999). All of these have obvious and significant disadvantages.

Evidence-based medicine is undoubtedly here to stay. Practitioners will increasingly need to feel comfortable with methodologies involving the assessment of the evidence. Despite the current limitations of the field, there are good reasons for accepting that this will ultimately benefit the practice of clinical psychopharmacology. The present volume rests on this assumption, and addresses the evidence-based psychopharmacology of each of the major psychiatric disorders.

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- Rush, A. J. (2001). Clinical practice guidelines: good news, bad news, or no news? *Archives of General Psychiatry*, **50**, 483–90.
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