Pharmacotherapy of Child and Adolescent Psychiatric Disorders

THIRD EDITION

EDITORS

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This book fulfills an urgent need for an updated text on pediatric psychopharmacology. It takes a unique approach in discussing recent findings within the context of current issues, including economic and political ones. The book covers the emerging question of treating children who do not yet meet diagnostic criteria for psychosis, e.g. schizophrenia or bipolar disorder, but who are deemed to be at high risk. This is an active area of debate: such children are being treated in certain centers, while others reject this completely. The book addresses the antidepressant controversy, the placebo response and unique strategies for delineating this, and ways to optimize the differential between active medication and placebo. It reviews the impact of recent American Heart Association guidelines for monitoring children on stimulants and other psychotropics with specific recommendations. It adheres closely to DSM-IV diagnostic criteria throughout. It describes the use of newly approved drugs such as Lexapro for treating adolescent depression and novel compound Intuniv and how it is prescribed. It covers the TADS and CAMS studies evaluating the use of SSRI's alone and in combination with cognitive behavioral therapy for adolescent depression. Other topics include treatment of bipolar disorders, increasing popularity of generic equivalents, combination pharmacotherapy and the potential dangers of psychotropic medications.

- Third edition of the first ever book published on pediatric psychopharmacology from renowned editors.
- Incorporates current developments with regard to SSRI's, their indications and their safety issues, including possible associated suicidal behavior.
- Addresses concerns about cardiovascular side effects of the new stimulant medications available, and compares to other FDA-approved medications for ADHD.
- Features many tables, figures and pictorials, making it highly accessible and reader friendly.

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FOREWORD BY NEAL RYAN MD
To J, Isa, the Henster and Foo—the reasons I smile inside and out.

David R. Rosenberg
Contents

List of Contributors, xv
Foreword, xix

Chapter 1 Historical Perspectives on Child and Adolescent Psychopharmacology, 1
Samuel Gershon
References, 4

Chapter 2 Pharmacoepidemiology of Psychotropic Medications in Youth, 7
Daniel J. Safer & Julie Magno Zito
Introduction, 7
Prevalence and trends for medications prescribed for ADHD, 8
Nonstimulant medications for ADHD, 11
Antidepressant medication, 11
Antipsychotic medication, 13
Alpha-agonists, 14
Anticonvulsant “mood stabilizers”, 15
Concomitant psychotropic medication, 15
Preschool psychotropic medication use, 17
International patterns of psychotropic medication for youth, 17
Conclusion, 18
References, 18

Chapter 3 Off-Label Prescribing of Drugs in Child and Adolescent Psychiatry, 25
C. Lindsay DeVane
Introduction, 25
Extent of off-label prescribing, 27
### Contents

Need for psychoactive drug treatments for children and adolescents, 31
Legislation supporting pediatric drug development, 33
Recommendations to follow when considering off-label prescribing, 35
References, 36

**Chapter 4 The Use of Generic Drugs in Pediatric Psychopharmacology, 39**
*Richard I. Shader & Christopher-Paul Milne*

What is a generic drug?, 39
Why are we discussing generic drugs?, 39
Basic requirements for generic drugs, 40
The status of regulations regarding generic drugs and children, 41
Abbreviated new drug application (ANDA) requirements, 42
Pediatric assessments of adult drugs (history up to current status), 43
Best Pharmaceuticals for Children Act, 44
Pediatric Research Equity Act, 45
Intersection of requirements for generics and pediatric assessment, 46
Future directions, 48
Concluding thoughts, 49
References, 49

**Chapter 5 Psychoactive Drug Use in Children: Basic Concepts in Clinical Pharmacology, 51**
*David J. Edwards*

Introduction, 51
Basic concepts in pharmacokinetics, 52
Dosing considerations for psychoactive drugs in children, 55
Summary, 60
References, 60

**Chapter 6 Psychostimulants, 65**
*Steven R. Pliszka*

Introduction, 65
Contents
xi

Epidemiology of stimulant use, 66
Structure and biochemical mechanism of action, 66
Neuroimaging studies of stimulant effects, 67
Studies of short-term efficacy, 72
Studies of long-term efficacy, 76
Clinical use, 79
Common side-effects, 84
Cardiovascular safety issues, 86
Growth suppression, 88
Substance use and diversion, 88
Comparison with nonstimulant treatment, 89
Treatment of comorbidity, 92
Pharmacogenetics, 93
Conclusions, 94
References, 94

Chapter 7 Tricyclic Antidepressants and Monoamine Oxidase Inhibitors for the Treatment of Child and Adolescent Psychiatric Disorders, 105
Charlotte M. Heleniak, Tejal Kaur, Kareem D. Ghalib & Moira A. Rynn
Tricyclic antidepressants (TCAs), 105
Drug interactions, contraindications, 116
Monoamine oxidase inhibitors (MAOIs), 117
General summary, 122
References, 123

Chapter 8 Selective Serotonin Reuptake Inhibitors (SSRIs), 131
Dara Sakolsky & Boris Birmaher
Pharmacokinetics, 131
Initiation and titration, 133
Indications and efficacy, 134
Adverse effects, 146
Withdrawal, 149
References, 149
Contents

Chapter 9 Novel (Atypical) Antidepressants, 155
Heidi R. Bruty, Graham J. Emslie & Paul Croarkin
Novel (atypical) antidepressants, 155
General overview, 155
Bupropion, 157
Duloxetine, 162
Mirtazapine, 164
Trazodone, 166
Venlafaxine, 170
Desvenlafaxine, 173
Alternative treatments, 174
Summary, 175
References, 176

Chapter 10 Antipsychotic Agents, 181
Brieana M. Rowles, John L. Hertzer & Robert L. Findling
Introduction, 181
Chemical properties, 182
Typical antipsychotics, 183
Atypical antipsychotics, 186
Ethical issues: treatment of at-risk populations, 212
Conclusions, 213
References, 213

Chapter 11 Lithium, 221
Garrett M. Sparks & David A. Axelson
Introduction, 221
Pharmacology, 222
Potential mechanisms of action, 222
Evidence for the use of lithium in children and adolescents, 232
Dosing and drug monitoring, 239
Contraindications, precautions, and drug interactions, 242
Side-effects, 246
References, 250
Chapter 12  Anticonvulsants Used in Child and Adolescent Psychiatric Disorders, 261
*Mani Pavuluri & Tushita Mayanil*

Introduction, 261
Divalproex sodium, 261
Carbamazepine, 271
Oxcarbazepine, 275
Lamotrigine, 279
Gabapentin, 284
Topiramate, 285
Conclusion, 288
References, 288

Chapter 13  Anxiolytics, 301
*Barbara J. Coffey & Amanda L. Zwilling*

Chemical properties, 301
Indications, 305
Contraindications, 320
Adverse effects, 321
Overdose, 324
Abuse/dependence, 324
Drug interactions, 325
Available preparations and cost, 325
Initiation and maintenance of treatment, 325
Management of specific side-effects, 330
How to withdraw medication, 332
References, 332

Chapter 14  Adrenergic Agents in Child and Adolescent Psychiatry, 341
*Lawrence David Scahill*

Clonidine and guanfacine, 341
Guanfacine, 349
Beta-blockers, 355
Acknowledgements, 361
References, 361
Contents

Chapter 15 Atypical Psychopharmacologic Strategies, 365
Jess Shatkin & Aron Janssen

Opiate antagonists, 365
Memantine, 368
Riluzole, 369
Secretin, 371
Topiramate, 372
Herbal medications and dietary supplements, 373
Ginkgo (*Ginkgo biloba*), 375
Melatonin, 381
Omega-3 fatty acids, 383
St. John’s wort (*Hypericum perforatum*), 384
Valerian (*Valeriana officinalis*), 387
Conclusion, 388
References, 389

Chapter 16 Psychopharmacology in Preschool Children, 399
Mini Tandon & Joan Luby

Introduction, 399
Developmental considerations, 400
Rise in psychopharmacology use, 402
Psychotherapy before psychopharmacology, 403
When psychopharmacology may be considered as a first line: pragmatic considerations, 404
Psychopharmacology in preschool disorders: administration and monitoring, 404
Off-label prescribing: special considerations, 407
Use of psychotropics in specific disorders, 408
Summary, 415
References, 415

Chapter 17 Combination Pharmacotherapy for Psychiatric Disorders in Children and Adolescents, 421
Gagan Joshi & Anna M. Georgiopoulos

Bipolar disorder, 422
Contents

Major depressive disorder, 429
Attention-deficit hyperactivity disorder, 431
Obsessive-compulsive disorder, 433
Tics and Tourette’s syndrome, 434
Pervasive developmental disorders, 434
Conclusion, 434
References, 435
Index, 439
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Foreword

It has been a decade since the publication of *Pharmacotherapy for Child and Adolescent Psychiatric Disorders*, Second Edition, by David Rosenberg, Pablo Davanzo and Samuel Gershon. New research over this decade has significantly changed the pharmacological and psychotherapeutic approaches to our most significant child psychiatric disorders. This new edition, therefore, has much that is new and important in our day-to-day clinical work.

Advanced psychopharmacology in children and adolescents is hampered by the paucity of studies and the relatively limited information that each separate study provides. Studies are expensive, research is difficult, and children are more complex to study than adults. Therefore, most but not all studies in youth address acute treatment in children with little comorbidity. Even in the most straightforward studies, we do not have the very large sample sizes that would give us narrow confidence intervals and the ability to ask meaningful questions about which subpopulations do best with which treatments. We also have little data on the comparative efficacy of treatments, even as first-line treatment of the acute disorder.

The questions that are more vexing and a larger part of our practice are, however, questions about how to treat refractory disorders, how to treat recurrent disorders, how to manage chronic medication use over years, and the risks of potential rare but serious side-effects. Studying these questions with adequate sample sizes is much harder and much more expensive. Guided by a few groundbreaking studies attempting to answer this sort of question in youth over the past decade, we will, nevertheless, frequently be forced to extrapolate from acute studies and from studies in adults. Not perfect but, like in most of medicine, we choose between Scylla and Charybdis. Most of us choose to extrapolate rather than nihilistically refusing to offer potential treatment to the difficult comorbid refractory youth that make up the majority of patients who come to us.

There has been remarkable progress in our field over the past decade. Few areas have been as fertile and active as the study of bipolar disorder in youth. We now have well-specified studies examining where the boundaries of this condition lie, testing the acute efficacy of a number of treatments particularly atypical antipsychotics, and comparing efficacy between different treatments. Research with antipsychotics in adults is
causing the field to question whether today’s atypical antipsychotics are indeed superior to first-generation compounds. We are starting to see psychotherapy studies in youths with bipolar disorder.

The past decade has brought us two large studies examining the combination of psychotherapy and pharmacotherapy in adolescent unipolar depression, a study of the treatment of adolescent unipolar depression, and a study of the treatment of adolescent depression refractory to initial SSRI treatment. We have also seen much more discussion of how to interpret studies with small effect sizes, questions about what the high acute placebo effect seen in unipolar depression throughout the lifespan means for our treatment strategies, and much thought given to the publication bias against negative studies and the (past) unavailability of data from negative studies on correctly understanding the aggregate meaning of studies. In addition, challenging questions have been raised about a potential increase in suicide with SSRIs and with other psychopharmacologic agents in youth.

Attention-deficit hyperactivity disorder has been a rich area of study over the decade. While stimulants are remarkably effective, other recent therapies including new long-acting stimulant preparations, atomoxetine, clonidine, and guanfacine, all have a role to play. Here, as in other areas of psychopharmacology, safety monitoring during treatment has received considerable attention.

This book examines in depth critical overarching questions for the field, including the pharmacoepidemiology of psychotropic use in youth, the use of medications for off-label indications, the role of advertising in consumer demand and medication use, and the question of possible use of medication treatment in prevention of disorders before first onset of the full syndromic picture.

Perhaps in another decade, Professor Rosenberg and colleagues will be able to tell us about new pharmacological treatments brought forth from bench-to-bedside translational research and about how genotyping or imaging approaches will truly let us tailor treatments to the individual. Until then, I expect this book will provide us with information critical to the care of youth with serious psychiatric disorders.

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CHAPTER 1
Historical Perspectives on Child and Adolescent Psychopharmacology

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The psychiatric treatment of children with drugs was essentially taboo until the 1990s, possibly due to the still major influence of psychodynamic views. This attitude presented a double-sided problem: there was a disinclination to administer pharmacotherapy to children who needed it and would benefit from it and, equally concerning, there was a vocal movement for mass treatment, underscoring a profound cultural shift. The media reported this widely, for example, in the article “Paxil, Prozac, Ritalin—are these drugs safe for kids???” [1]. It was thus commonplace to read that parents and schools were just searching for a quick fix for behaviors that fell outside the “norm.” Ritalin had been available since 1954, and so perhaps the acceptance of psychopharmacology as an intervention sped the clock on the acceptability of pharmacological agents to deal with behaviors outside the new cultural norms. These treatment options claimed to offer the possibility for any child who fell outside these behavioral “norms” to be “improved.” Thus, a market force developed that underpins the efforts of pharmaceutical companies to develop their products. Although controversial, these concepts have expanded recently to suggest that early diagnosis of psychiatric disorders such as schizophrenia and bipolar disorder may warrant the initiation of pharmacotherapy at the earliest manifestation of “prodromata” of these conditions.

Stimulants may well have been the first entrants into child pharmacotherapy. Amphetamine was resynthesized in the US in the 1920s and had been employed as a respiratory stimulant for narcolepsy and as an appetite suppressant. By 1937 it was shown to be an effective treatment for hyperactivity in children by Charles Bradley [2]. Later others also reported on the efficacy of Ritalin in children with hyperactive states. Its
effectiveness led to the acceptance of the concept of minimal brain dysfunction, which in 1980 in DSMIII was categorized as attention-deficit hyperactivity disorder (ADHD).

Psychopharmacological treatments have been introduced in large part as the result of serendipitous events. The earliest agents included lithium, chlorpromazine, and imipramine. They gradually developed a role in the treatment of adult patients and then were tried in pediatric patients by deduction of the possible similarity of these behaviors to those established in adults. There are many assumptions in this last step to the treatment of children. For example, imipramine and related compounds were indeed quite effective for major depressive disorder in adults. However, their translation to children implied an essential assumption that the depression seen in children was analogous to that seen in adults, and that the underlying substrate would respond similarly. Whatever the assumptions, the outcome belied these assumptions, as the careful studies of Ryan et al. [3] clearly demonstrated. Here we had a cautionary tale and we have not fully explained this outcome and the assumptions inherent therein. Thus we must move cautiously before we presume such simple projections from adults to children.

Then there developed a period of major enthusiasm for two new classes of psychotropic agents: the selective serotonin reuptake inhibitors (SSRIs) and the atypical second-generation antipsychotics (SGAs). As before, their usage was explored initially in adults with the SSRIs becoming widely employed for depressive disorders and pretty much completely displacing the tricyclics. Both classes of drugs were then extensively prescribed for children and adolescents. Following the FDA’s warnings, with black-box and bold-print cautions, there has been a significant reduction in their prescriptions. Associated with this is the hotly debated issue of suicidality associated with these antidepressants.

Some of the SGAs have also caused serious concern because of the increased risk of metabolic syndrome with significant weight gain and the concurrence of type-II diabetes. These adverse effects produce a very special risk in developing children. These few instances provide adequate warning about a transfer of psychopharmacological drug prescribing from adults to children. There is now clearly the need, which has been recognized, for the careful clinical evaluation of new agents for specific indications in children.

The prevention and treatment of emotional and behavioral problems affects about one in five children and is the major mental health problem in the United States. Most major mental health problems begin during adolescence. Therefore, this is the critical period for their identification, prevention and often their treatment. Suicide among the young has become an increasing concern over the past several decades. It is important
to consider, within this context, the high rate of suicide in the young inductees in the armed forces. Another aspect of this issue has come up over the past 10 years and that has been the possible effects of administering antidepressant drugs to children and adolescents and the concerns that were raised about possible increase in suicidal outcomes. All these questions have increased the importance of the optimal methods of treatment of depression in these populations.

This third edition of pharmacotherapy for child and adolescent disorders is being published 10 years after the first edition. Although the field has advanced considerably, the fact that we are dealing with a still-developing nervous system presents both special options and serious cautions. The use of psychotropic agents in adults has become well established since the 1960s and the picture of their clinical indications and side effect profile has become much clearer. These issues are still not so well defined in children, as their diagnostic entities are still being delineated and thus specific therapies are also under debate. The social and cultural background for the acceptance of psychotropic interventions has altered over the years. Initially, they were considered inappropriate, dangerous and treatments of last resort for children. Society has changed its attitude dramatically and now there is a serious concern of overmedication of children. Thus, although the field has progressed significantly, the appropriate administration of psychoactive medications to children requires training, skill and ongoing interaction with the patient and family throughout the course of treatment.

This is especially the case as many more drugs have been introduced and their indications and profile of actions are still in progress. The basic research studies on their mode and site of action will continue to provide the field with knowledge, which will help considerably in their more targeted usage. The question of early usage of therapeutic interventions in some of these conditions has been raised, offering the possibility of preventive value. This early and possibly long-term usage raises new and important questions in regard to short- and long-term possible adverse effects on developing systems.

Early intervention for all medical or psychiatric disorders is essentially always considered beneficial. However, with psychiatric disorders in children, especially in the younger age groups, the prospective identification of prodromata has been and still is problematic. Various investigators have presented studies on this problem, such as the proposal of “ultra high risk” (UHR) criteria [4]. One still unresolved problem is the potential effects of the various psychotropic drugs on the developing nervous system and other organ systems, especially if administered long term, as is often necessary in a number of disorders. Adverse neurocognitive effects of psychotropic medications have been reported [5, 6]. For example,
4 Pharmacotherapy of Child and Adolescent Psychiatric Disorders

GABAergic agonists have been demonstrated to interfere with both mood and memory, as well as attention and psychomotor speed. Thus, there is a debate about early psychopharmacologic intervention in children. Specifically, it concerns the issue of whether the impact and consequences of lack of treatment outweigh the potential for prematurely labeling children with emotional disturbances. In this population of children and adolescents, early clinical features can also be difficult to distinguish from benign conditions and normal experience. These concerns cannot easily or speedily be resolved. The question of the diagnosis of these psychiatric disorders is still being evaluated for DSM V. Good data on the long-term use of psychotropic agents both on body organs and the central nervous system are still incomplete in young developing systems. Therefore, we believe we can only raise a cautionary note and await further data on both aspects of this question. Hopefully we will have a resolution by the time we come to the fourth edition of this volume.

All of these activities in the field have contributed to the creation of this third edition. It is hoped that this volume will serve as a valuable guide to the treatment of patients 18 years of age and under with psychiatric disorders. This volume is presented as a practical guide to the clinical psychiatrist. The book also provides valuable material for other health care professionals in the management of children and adolescents with psychiatric conditions. The material presented here is in a format readily available for psychologists, social workers, therapists, nursing staff and students, as well as medical students, pediatricians and family practitioners. We felt that a brief historical review of the background of the development of psychopharmacological interventions in children could provide a frame of reference for the developments and practices in the field today. It should also provide a perspective that the field is and should be changing. We have delineated what is known currently on the basis of a critical review of controlled trials available. We have also attempted to integrate the basic neuroscience available to help guide clinical decision making.

References

Historical Perspectives on Child and Adolescent Psychopharmacology


CHAPTER 2
Pharmacoepidemiology of Psychotropic Medications in Youth

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Introduction

Pharmacoepidemiology
A major function of pharmacoepidemiology is to analyze large computerized datasets in order to reveal patterns of medication treatment in community populations. Such analyses are commonly used to estimate prevalence, persistence of use, correlates, and trends in treatment. These measures of utilization are developed from various sources including: (1) Medicaid reimbursement claims [1–3] and state children’s health insurance program (s-CHIP) claims from higher income public insurance enrollees [4]; (2) Health Maintenance Organization (HMO) records [5–7]; (3) commercial insurance data from multiple data files [8] and from pharmacy benefit managers (PBMs) [9, 10]; (4) national population surveys of office visits, such as National Ambulatory Medical Care Surveys (NAMCS) [11, 12] and population surveys of patient-reported service use, such as Medical Expenditure Panel Surveys (MEPS) [13]; (5) school and community surveys [14, 15]; (6) state controlled substance data bases [16]; (7) federal production quota data on controlled substances [17]; (8) prescription sales data [18]; and (9) population-based cohort studies to assess treatment outcomes [19, 20]. Finally, data on the unintended effects of medications can be analyzed from the FDA Adverse Drug Event (ADE) Reporting System (AERS), which consists of voluntary reports of ADEs from physicians, manufacturers and the community [21]. Collectively, these sources produce a mosaic of U.S. patterns of psychotropic use and treatment-emergent adverse events which may differ across region,
socioeconomic class, and other broad dimensions of population health that are not reflected in clinical trial populations or in case series reports.

**Strengths of pharmacoepidemiology**
Community datasets include all eligible, enrolled or surveyed individuals, not only those who seek treatment. Thus, total enrollees are all those surveyed from the denominator, which is the foundation for the prevalence of use in a population-based estimate. Demographic information, outpatient services, and other relevant variables are commonly linked to the medication dataset. The linkage permits stratification on numerous correlates including race and ethnicity (from Medicaid and federal surveys only), age group, gender, region of residence, Medicaid eligibility category, private insurance, and the presence of psychiatric or chronic comorbidities. Various outcomes beyond summary prevalence measures are being used—for example, measuring concomitant between- and within-drug class treatment (more than one psychotropic class or drug entity simultaneously), assessing drug-related laboratory monitoring data, and measuring persistence (days) of treatment.

**New methods used in pharmacoepidemiology**
In the last decade, new methods have been applied to drug data alone and linked to other health services. First, in contrast to prevalent user methods, new user methods measure newly initiated drug therapy [22,23] and this approach has been increasingly used to more precisely assess the temporal effect of regulatory changes, for example boxed warnings on antidepressant labels [23]. Second, multivariate data analyses can correct for extrinsic influences on practice patterns and establish odds ratios (measuring the probability of use relative to a reference group). Third, the persistence of drug treatment is a measure of duration of use from large datasets as a surrogate for medication adherence.

**Focus of this update**
This chapter will focus on: (1) psychotropic medication trends in relation to psychiatric diagnosis; (2) frequently or increasingly used classes, for example, stimulants, antidepressants and antipsychotics; (3) the use of several classes concurrently (concomitant treatment); (4) the preschool age group; and (5) international differences in prevalence of medication use.

**Prevalence and trends for medications prescribed for ADHD**

From parent reports in the National Health Interview Survey conducted by the Center for Disease Control (CDC) in 2003 and 2007, the prevalence