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David M. Gardner and Michael D. Teehan
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Antipsychotics and their Side Effects

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**We dedicate this book first and foremost
to people, patients, and families affected
by mental illness. It is also dedicated to those
who direct their energy, knowledge, and skills
to advocate and care for them.**

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Foreword

Antipsychotics and their Side Effects is authored by Professor David M. Gardner, Department of Psychiatry and College of Pharmacy, and Associate Professor Michael D. Teehan, Department of Psychiatry, Dalhousie University, Halifax, Canada. The authors are highly experienced clinicians with strong academic interests that include expert knowledge of antipsychotic drugs. Their book is divided into three sections: (i) 20 chapters with references and tables on adverse effects of antipsychotic drugs (including hematological, anticholinergic, metabolic, neurological, ophthalmological, cardiovascular, dermatological, sexual, and urinary effects, and changes in vital signs), emphasizing the adverse effects in relation to specific drugs, with tabulated recommendations about monitoring; (ii) tabulated specific recommendations and guidelines for monitoring individual drugs (aripiprazole, chlorpromazine, clozapine, flupenthixol, fluphenazine, haloperidol, loxapine, methotrimeprazine, molindone, olanzapine, paliperidone, pericyazine, perphenazine, pimozide, pipotiazine palmitate, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, ziprasidone, and zuclopenthixol); and (iii) guidelines for eliciting information from patients, including the use of novel assessment forms to monitor for adverse effects during treatment with antipsychotic drugs, with the implicit aims of limiting risk of adverse effects and facilitating timely clinical interventions. The material compiled is solidly grounded on findings from the research literature.

A major motivation for writing this book is the authors' stated impression that the second-generation antipsychotic drugs have brought limited clinical advances in efficacy for the treatment of psychotic, manic, and other disorders over the first-generation neuroleptics that have entered clinical psychiatry

since the early 1950s, although with dissimilar patterns of adverse effects. The newer antipsychotics brought variable reductions in risk of some adverse neurological effects but their own set of complex metabolic and other risks. In turn, Drs. Gardner and Teehan call for dealing with this complexity by particularly active and thoughtful monitoring for a broad spectrum of adverse effects that are addressed systematically in this book. Their approach is particularly timely, as contemporary clinical psychiatry – no doubt encouraged by the substantial, if partial, success of pharmacological treatments for many disorders – appears to be tending increasingly to devalue traditional clinical skills, with the risk of more brief, superficial, and technical approaches to clinical therapeutics. Interactions with patients sometimes seem surprisingly impersonal and far from psychiatry's tradition of centering the patient–clinician interaction on the views and experiences of individual patients. This book should contribute to limiting such trends.

The modern era of clinical psychopharmacology can be dated from the introduction of lithium carbonate for mania and then for long-term prophylaxis in manic-depressive (bipolar) disorder in the late 1940s, and of chlorpromazine for the treatment of mania and acute psychosis, and later for chronic psychotic disorders including schizophrenia in the early 1950s. These largely serendipitous advances initiated major, even revolutionary, changes in psychiatric diagnostics as well as therapeutics [1]. However, the story of modern antipsychotic drugs only in part is about scientific innovation and rational application of principles arising from basic neuroscience, neuropharmacology, medicinal chemistry, and rational therapeutic experimentation [1–3]. In addition, it is characterized by powerful sociological trends. These include a degree of wishful overvaluing of the new treatments, and of disinclination to face squarely the limitations and considerable clinical problems associated with this class of palliative drugs. Even such terms as “side effect” and “atypical” with respect to antipsychotic drugs are problematic, and euphemistically suggest occasional minor costs to be balanced against consistent major clinical benefits.

In reality, the benefits of antipsychotic drug treatments often are modest, at least in chronic psychotic disorders including schizophrenia, delusional disorders,

schizoaffective conditions, and in the dementias. Even their more striking benefits in mania and acute psychotic syndromes typically require weeks or even months for full symptomatic remission, and they often fail to provide substantial benefit for cognitive and functional status at any time. In turn, this is a story of business and marketing in a multibillion dollar per year industry. Importantly, all of these developments have had an important impact on the shaping of modern psychiatric practice, with growing emphasis on standardization and purported “efficiency,” largely driven by a desire to limit clinician time and costs. In a more salutary direction, the book further implies that the range and complexity of adverse clinical effects of antipsychotic and other psychotropic agents encourage renewed interest in general medicine among psychiatric clinicians.

It is to be hoped that choices of drugs, doses, timing, and duration of treatment would arise primarily from the clinically interpreted outcomes of randomized, controlled, and well-designed and managed clinical trials. However, for now, such evidence with respect to the antipsychotic drugs is very limited. With the probable and still-unexplained exception of clozapine (an older drug, first patented in 1960), most older and newer antipsychotic drugs are indistinguishable from one another with respect to efficacy in short-term controlled trials, or in long-term clinical effectiveness. All antipsychotics currently employed clinically or commercially have passed regulatory requirements of showing evidence of some degree of efficacy or statistical superiority to a placebo or no active treatment. Sometimes, the benefits are only a few percentage points above outcomes associated with a placebo: statistically “significant,” but often of marginal clinical superiority, particularly in the continued or even new treatment of chronic psychotic disorders including schizophrenia. It remains extremely challenging to rank specific drugs by their likelihood or degree of clinical benefits. Although older and newer antipsychotics are remarkably similar in efficacy, the newer and far more expensive agents have been marketed aggressively and very successfully. Most of them do have substantially or even markedly reduced risks of certain adverse neurological effects, particularly acute dystonias, parkinsonism, and perhaps tardive dyskinesia, with continued risk of akathisia, but less or altered

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presentations of neuroleptic malignant syndrome as delirium and unstable vital signs, but far less muscle rigidity than with most first-generation neuroleptics [1].

In addition, the substantial but limited efficacy of most psychotropic drugs, coupled with powerful but often exaggerated iatrogenic expectations supporting their use, has encouraged increasingly complex and largely non-rational, or at least untested and unproved, applications of combinations and higher doses of drugs, including the antipsychotics. In turn, these trends can increase risks of sometimes unpredicted drug interactions and of adverse effects, even when individual drugs are prescribed at moderate doses [4,5].

An important theme of this book is that the important but partial benefits of the antipsychotic drugs as a class need to be balanced against their considerable risk of adverse metabolic, neurological, and other unwanted general medical effects [5,6]. It is particularly ironic that some of the most effective antipsychotic agents, such as clozapine and olanzapine, are complicated by a range of potentially severe or even life-threatening adverse medical effects. In the absence of clear, evidence-based differences in efficacy of most antipsychotics, such adverse-effect risks can usefully guide selection of drugs and doses for individual patients, with the aim of limiting risks. These risks range from the clinically incidental to severely uncomfortable, sometimes disabling, and occasionally lethal effects. The search continues for a scientific basis of rational psychiatric therapeutics based on research evidence of differences in efficacy among specific drugs, as a component of “evidence-based medicine.” Progress to that aim would be greatly facilitated by head-to-head, direct, randomized comparisons of different agents or doses to test comparative efficacy directly. However, for now, individualized assessments of the impact of adverse effects, and the large variance in acquisition costs of individual drugs, arguably, are more significant factors in drug selection than differences in efficacy.

In short, the often minor or subtle differences in clinical benefits among specific antipsychotics make adequate understanding of the nature, recognition, and avoidance or amelioration of their adverse effects all the more important. Selection of drugs and doses

that are well tolerated by individual patients is highly dependent on an informed clinician, alert to emerging signs and symptoms and, perhaps most important, of subjective distress that requires some effort and attention to elicit from each patient. These downsides of the clinical use of this important class of psychotropic drug are addressed comprehensively, thoughtfully, and critically by this book. In short, it is a valuable and timely teaching and reference work.

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Preface

The impetus to writing this book was, at first, local. In our academic center, psychiatrists and other clinicians involved in caring for patients with mental illnesses were in a quandary. The first wave of enthusiasm coming from the introduction of a new generation of antipsychotic medication was ebbing. The relief experienced in prescribing antipsychotics relatively free of the specter of disabling movement disorders was being tempered by new concerns. *Time* magazine cover stories and the marketing arms of pharmaceutical companies had fuelled expectations that were sagging in the face of clinical experience. Clinical trials of limited scope, some with overt biases in their design and analyses, were being more closely scrutinized and reconsidered. Critical appraisal of the whole field was raising disturbing questions about the measurable benefits from the introduction of expensive replacements for first-generation (conventional) antipsychotics. The increasingly irreconcilable claims of Pharma-sponsored work, research findings from publicly sponsored trials, and clinical experience created not only confusion but disappointment among clinicians in the trenches.

There were nagging questions in the air. Had we prematurely abandoned some very effective and trusted remedies, imperfect as they were? Did the new agents truly improve the quality of our patients' lives? Was the difference, if any, from the effects of the older agents worth the considerable increase in cost to the healthcare system and to our patients? Most worrying of all to clinicians was the question of whether we had substituted an equally damaging set of side effects for the familiar hazards of haloperidol and chlorpromazine.

There is a well described arc of activity with the introduction of new pharmaceuticals to the marketplace. Initial expectations drive a surge of switches from current treatment in resistant cases, and desperation promotes off-label use. This novelty phase begins to fade as failure of the new drug in poorly selected uses inevitably disappoints. The emergence of unexpected adverse events, not anticipated by the limited samples in clinical trials, emerges concurrently. Clinicians begin to focus selection of the new drug more finely and are more watchful for newly recognized adverse effects. At this point, growth in use of the medication is resumed but at a more measured pace. After several years, a niche is eventually found for the new agent.

We began to write these guidelines for monitoring antipsychotics at the end of the first wave of use. Clinicians have not found the second-generation (atypical) antipsychotics to be transformative for their patients. They do not improve the lives of all patients, and in some instances they worsen outcomes. The reality of a new set of adverse effects has become painfully obvious.

On the other hand, many patients have responded very well and have found the new medications to be more acceptable than their older treatment. The risk of acute, frightening extrapyramidal dysfunction in the early phase of treatment has been markedly but not entirely eliminated. Eventually, most patients were stabilized on their new regimens and were somewhat content with the change.

For many seasoned clinicians, however, simplicity had exited the scene. The comfort of defaulting to the same options among the original agents, which had spanned two generations of prescribers, had been replaced with the uncertainty of choice and with it a new set of concerns. The careful monitoring of treatment, with most attention focused on movement disturbances, no longer sufficed. A whole new area of concern had sent clinicians scrambling to retrieve their general medicine texts and to update themselves about metabolic disorders that had last concerned them as interns. It became clear to many that the physical health of their patients was suffering and their care was falling through the cracks. What should be monitored, how, when, and most importantly who should do

it have become questions challenging all who care for patients using antipsychotics.

As new concerns about the metabolic and other effects of the newer agents grew, older concerns faded and with them so did the skills of detection and treatment. New practitioners have rarely been exposed to the once common features of antipsychotic use. Senior residents report that they have seen very few cases of cogwheel rigidity and doubt if they could efficiently and effectively complete a standard physical assessment for the extremely well-characterized neurological adverse effects of antipsychotics. New practitioners have said that they were never taught these skills and experienced practitioners acknowledge that they are losing or no longer using them.

The end result for patients of the switch in prescribing trends, from first- to second-generation antipsychotics, is that they are being followed within a broken monitoring system that desperately needs remediation. Older, well-developed skills of assessment and monitoring need to be revitalized and at the same time new practices need to be implemented such that the safe and effective use of older and newer antipsychotics can be optimized.

Communications and planning merit special attention. Knowing how to detect and monitor antipsychotic side effects is not enough. Many patients see several physicians and other healthcare providers who are capable of monitoring their response to antipsychotics. Determining who is responsible for what, when it comes to monitoring patients taking antipsychotics, requires planning and ongoing communications among the patient's healthcare providers. Without this important clarification, systemic problems will not be resolved.

Our textbook will not address, let alone resolve, the many systemic challenges. However, it can serve as an accessible and informative resource of what to do, when to do it, and how to do it. It is designed to be a reference tool and to facilitate decision-making for optimal monitoring for people who are prescribed antipsychotic medications. We recognize the practical impediments to fully upholding these expectations (gaps in knowledge, lack of capable personnel, unwilling patients, time constraints, and fiscal limits). While

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acknowledging these challenges, we have tried to identify, describe, and guide comprehensive monitoring of clinically relevant adverse effects of antipsychotics. As is the practice in many areas of medicine, systematic monitoring provides the greatest safeguards. We propose a structured follow-up plan in each case, using

standard measures, applied at defined intervals, to detect adverse effects and to monitor them regularly. The aim is to provide clinicians with a means of providing optimal, safety-oriented care to patients who are followed over lengthy periods. Who carries out this work and how it is done, we entrust to you.

Acknowledgements

This book represents the culmination of several years of effort and important contributions by numerous individuals. Approximately 6 years ago, recognizing the poor overall follow-up care that many of our patients were receiving, we embarked on a project as co-chairs to develop a comprehensive monitoring guide for Nova Scotia's Capital District Health Authority (CDHA). The aim of the guide was to improve the monitoring of patients, hospitalized and ambulatory, who were being treated with antipsychotic medications long term. Many of the ideas generated while developing the antipsychotic monitoring guide are reflected in this book and our gratitude goes to those who supported the development of the monitoring guide. Dr. S. Devarajan, Julie Garnham, Susan MacLellan, Dr. Heather Milliken, and Barbara O'Neill were members of the steering committee for the project, and Christopher Daley, Derek Roberts, Sheri Axworthy, Loa Barendregt, Fady Kamel, Christopher Dolan, Kathy Ann Turner, and Rochelle Myers, who were pharmacy and medical students at Dalhousie University and the University of Toronto, provided research assistance in the development of the CDHA monitoring guide. Without their dedicated and industrious help to the CDHA project, this book would never have materialized. During the final year of her psychiatry residency, Dr. Linda Hoyt developed the initial simplified antipsychotic monitoring form, which was tested with the cooperation of Dr. Edward Gordon and inpatient staff and patients. An updated version of this form can be found in this book. Financial support for the CDHA monitoring guide was provided by means of arms-length, unrestricted educational grants from multiple pharmaceutical companies including AstraZeneca, Janssen-Ortho, Eli Lilly, Novartis, and

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Purpose, development, and limitations of *Antipsychotics and their Side Effects*

Purpose

The possible side effects of antipsychotics are extensive, varied, frequently intolerable, too often serious, and sometimes fatal. Clinicians cannot be expected to use these drugs optimally in the care of their patients when inexperienced with the antipsychotic prescribed or unfamiliar with the adverse possibilities and how to monitor for them. This book aims to support clinicians in improving the safe, long-term use of antipsychotic drugs by their patients. Specifically, this book is designed to (1) help inform antipsychotic treatment selections for individual patients (Section 1); and (2) support monitoring of antipsychotic-related side effects over the course of therapy (Sections 2 & 3). For more details, refer to the Guide to using *Antipsychotics and their Side Effects* on p. xx.

Antipsychotics and Their Side Effects was developed as a comprehensive, extensively referenced resource following a semi-systematic approach using three main sources of information: (1) the best available evidence; (2) identification of best practices; and (3) incorporation of our clinical and expert opinion.

Development

There is little or no research that directly assesses the best methods for the monitoring of antipsychotic treatment tolerance or safety. However, selected research and information on the effectiveness, tolerability, and

safety of antipsychotics can be used to develop appropriate monitoring practices. Extensive effort was made to locate and review this information. Aided by our research assistants, we conducted searches and literature reviews. Electronic resources used were Medline, EMBASE, the Cochrane Library, PsycINFO, Web of Science, Micromedex Drug Information, and reports from regulatory authorities (e.g. the US Food and Drug Administration, Health Canada). Drug monographs from antipsychotic manufacturers as well as from independent sources (e.g. AHFS Drug Information) along with specialty references (e.g. Meyler's *Side Effects of Drugs* and Joseph and Young's *Movement Disorders in Neurology and Neuropsychiatry*) and health technology assessments were used as appropriate to identify tolerability and safety information. Clinical practice guidelines and published monitoring recommendations were also reviewed. When several studies were identified that addressed the same issue (e.g. diabetes risk with antipsychotic use), the best available evidence as determined by the hierarchy of evidence was selected and used to inform the content.

Limitations

The book offers a unique and clinically valuable resource but is not in itself sufficient for achieving its goals, which are tied directly to the clinician's monitoring practices and systemic supports for monitoring.

Most monitoring recommendations in this book do not derive from studies that were designed to identify the most efficient or effective method for monitoring antipsychotic-related adverse effects. Such studies are effectively non-existent. Rather, the recommendations are a result of several informative components including an assessment of evidence of the risk, frequency,

and timing of adverse effects caused by antipsychotics, an assessment of various methods to detect these potential harms, and our clinical judgement.

This guide does not provide information or advice regarding the management of antipsychotic-related adverse effects. The management (or preferably the prevention) of these adverse effects is of critical importance; however, it is beyond the scope of the book. It also does not provide guidance on how to monitor for the desired effects of antipsychotic treatment or what to do if not achieved. For this you are referred to the appropriate clinical practice guideline. This edition also does not specifically review the potential side effects of switching or stopping antipsychotics or how to monitor for them. The information provided applies generally; details related to the side effects and monitoring of antipsychotics when used in unique patient populations, such as the very young and old or during pregnancy and lactation, are not the focus.

The book is intended to supplement good clinical care practice. However, it should not be considered complete in its coverage of potential adverse effects related to antipsychotics or in its recommendations for detecting and monitoring potential adverse effects for all patients. Adjustments or additions to the recommended monitoring may be required for selected patients; for example in pediatric and elderly patients, those on complex drug regimens, or for those with communication limitations. Moreover, application of the information in this guide may not limit or prevent the occurrence of minor or serious adverse effects related to antipsychotics. Users of this book are expected to use their training, knowledge, and judgement regarding the care of their antipsychotic-treated patients in an effort to achieve the desired benefits of treatment while minimizing the treatment-related harms. The guidance offered in this book is not written for non-practitioners.

Guide to using *Antipsychotics and their Side Effects*

This book was developed to support healthcare professionals involved in the care of patients receiving antipsychotic drugs long term. It is hoped that this book will be useful for psychiatrists, family practitioners, nurses, pharmacists, and mental healthcare workers. Some components of the book will also be of benefit to other health professionals, including dietitians and other medical specialists, during their care of patients receiving antipsychotics. Although this book was not developed for patients or their families, they too may find the content useful for making informed treatment decisions and for monitoring guidance.

This book has three major sections, each having a unique clinical utility. Section 1 includes the introduction and 20 concise chapters describing antipsychotic side effects along with the related monitoring recommendations. Each chapter begins with background information about the problem and then provides a summary of the evidence related to specific antipsychotics. General information on how to monitor for the problem, including in some instances how to interpret clinical observations or laboratory results, is provided, followed by an antipsychotic-specific monitoring schedule. Each chapter's monitoring recommendations are consistent in terms of the proposed schedule, and the same symbols are used throughout. These chapters can be used by practitioners to help select an antipsychotic for a specific patient based on the comparative risks for various adverse effects among the different antipsychotics. It also supports practitioners in identifying reasonable methods for the monitoring of adverse effects.

For Section 2, we have created individual antipsychotic monitoring monographs, presented in alphabetical order, that provide clear monitoring recommendations for each antipsychotic. Each monitoring monograph is a reorganization of the information found in Section 1 such that practitioners can easily identify what to monitor and when for each individual antipsychotic. This section of the book will be most useful once the practitioner has selected an antipsychotic and wishes to put a monitoring schedule in place.

In Section 3, we have attempted to distill and somewhat simplify the monitoring recommendations from Sections 1 and 2 into a single general monitoring form that covers most antipsychotic side effects included in the book. To do this, we had to make some compromises, as the monitoring requirements of a patient taking one antipsychotic can be quite different from those when taking a different antipsychotic. However,

we recognize that a general, non-specific monitoring schedule is better than no schedule at all. The monitoring form offered should be combined with the monitoring schedule suggested for the specific antipsychotic prescribed (see Section 2). Moreover, and of critical importance, the clinician should use his or her judgement in modifying the monitoring guide to meet the patient's health needs. Upon first reviewing the form, we expect that it may appear demanding and a bit unclear. To help with the latter, we have provided a guide on how to use the form. To address the concern that the monitoring recommendations may be too demanding, we encourage you to try it out for three to five patients and then determine if it is too demanding or not. We hope your ultimate decision about the value of the form will come from experiencing it. If you would like to create copies of this form and/or would like to adapt it to your needs, it can be downloaded at **www.cambridge.org/9780521132084**.

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About the cover art

Ruthmarie Adams is a self-taught artist and resident of Halifax, Nova Scotia, Canada. She was 26 years of age when she painted this image simply titled *Depression*. It is based on her personal understanding of mental illness. Ruthmarie described the woman in the painting as feeling overwhelmed, lost, and confused. She added, “In the midst of a mental illness the affected person’s voice is often not heard. This is symbolized in the painting by the blurred mouth.” As a social worker, Ruthmarie supports individuals with mental health challenges to build work skills and the necessary confidence to re-enter the workplace.

