Michael S. Ritsner *Editor*

# Polypharmacy in Psychiatry Practice

## Volume II

### Use of Polypharmacy in the "Real World"

Springer

Polypharmacy in Psychiatry Practice
Volume II

Michael S. Ritsner
Editor

# Polypharmacy in Psychiatry Practice
# Volume II

## Use of Polypharmacy in the "Real World"

Springer

*Editor*
Michael S. Ritsner
Technion - Israel
Institute of Technology
Sha'ar Menashe Mental Health Center
Hadera, Haifa, Israel

ISBN 978-94-007-5798-1 ISBN 978-94-007-5799-8 (eBook)
DOI 10.1007/978-94-007-5799-8
Springer Dordrecht Heidelberg New York London

Library of Congress Control Number: 2013932219



Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

*I dedicate this book to my dear grandchildren Ron, Miriam, Diana and Daniel Ritsner who are funny, smart, obstinate, and sometimes downright willful*

# About the Editor

**Michael S. Ritsner, M.D., Ph.D.**

**Dr. Ritsner, MD, PhD** is a physician and scientist who spent his career of over 35 years caring for patients and studying the nature and treatment of mental illness. Dr. Ritsner is a Professor of Psychiatry at the Rappaport Faculty of Medicine, Technion – Israel Institute of Technology (Haifa), Israel.

Dr. Ritsner graduated from the Khabarovsk State Medical University, and received his PhD in Psychiatry from the Siberian State Medical University in 1975 (Tomsk, Russia). After gaining clinical practice as a neurologist and clinical psychiatrist he joined the Siberian State Research Center at the Russian Academy of Medical Sciences (Tomsk) as a Head of the Psychiatric Genetics Department in 1981. In 1990 he emigrated to Israel where he chaired a Psychiatry Department and the Research Unit at Talbieh Mental Health Center (Jerusalem). Since 1998 Dr. Ritsner directs the Acute Department of the Sha'ar Menashe Mental Health Center, and Cognitive & Psychobiology Research Laboratory affiliated to the Rappaport Faculty of Medicine, Technion.

Particular areas of interest include schizophrenia spectrum disorders, genetic epidemiology, neuropsychiatric biomarkers, the role of neurosteroids in schizophrenia, novel neuroprotective treatments, and cognitive and quality of life impairments. Dr. Ritsner's research has been supported by grants from the Stanley Foundation. He also currently serves as Principal Investigator of a multi-site research team searching and testing novel agents with neuroprotective properties for treatment of the debilitating effects of schizophrenia and related psychotic disorders.

Dr. Ritsner is the co-author of two books on neuropsychiatry and editor of three books and two handbooks, and has published more than 140 peer-reviewed journal articles, reviews, and more than 20 book chapters. He has given more than 200 presentations including as invited speaker at scientific conferences and medical education events.

This monograph is yet another milestone toward achieving his goals of providing a comprehensive up-to-date state-of-the-art overview of the literature that addresses the challenges facing clinical and biological psychiatry. This series follows 12 volumes:

1. *Quality of Life Impairment in Schizophrenia, Mood and Anxiety Disorders. New Perspectives on Research and Treatment*. Ritsner, Michael S.; Awad, A. George (Eds.), Springer, Dordrecht. The Netherlands, 2007, 388 p.
2. *Neuroactive Steroids in Brain Functions, and Mental Health. Novel Strategies for Research and Treatment*. Ritsner, Michael S.; Weizman A. (Eds.), Springer Science + Business Media, B.V., 2008. 559 p.
3. *The Handbook of Neuropsychiatric Biomarkers, Endophenotypes, and Genes*. Volumes I–IV. Ritsner, Michael S. (Ed.), Springer Science + Business Media, B.V., 2009.
    - Volume I: *Neuropsychological Endophenotypes and Biomarkers*. 231 pp.
    - Volume II: *Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers*. 244 pp.
    - Volume III: *Metabolic and Peripheral Biomarkers*. 231 pp.
    - Volume IV: *Molecular Genetic and Genomic Markers*. 232 pp.
4. *Brain Protection in Schizophrenia, Mood and Cognitive Disorders*. Ritsner, Michael S. (Ed.), Springer Science + Business Media, B.V. 2010. 663 p.
5. *Handbook of Schizophrenia Spectrum Disorders*. Volumes I–III. Ritsner, Michael S. (Ed.), Springer Science + Business Media, B.V. 2011.
    - Volume I: *Conceptual Issues and Neurobiological Advances*. 494 pp.
    - Volume II: *Phenotypic and Endophenotypic Presentations*. 526 pp.
    - Volume III: *Therapeutic Approaches, Comorbidity, and Outcomes*. 461 pp.
6. *Polypharmacy in Psychiatric Practice*. Volumes I–II. Ritsner, Michael S. (Ed.), Springer Science + Business Media, B.V. 2013.

Dr. Ritsner served as Associate Editor, *Quality of Life Research* (an international journal of quality of life aspects of treatment, care and rehabilitation, Amsterdam, The Netherlands); Board Member, *American Journal of Neuroprotection and*

*Neuroregeneration* (USA); *CNS & Neurological Disorders-Drug Targets* (Italy); and member of the Scientific Committee, International Society for the Study of Neuroprotection and Neuroplasticity (Romania). Referee activity: *CNS Drugs*, *Quality of Life Research*, *Psychiatry Research*, *Clinical Drug Investigation*, *Social Psychiatry and Psychiatric Epidemiology*, *Biological Psychiatry*, etc.

Web: http://md.technion.ac.il/lecturers/lecturer_desc.asp?lecturerID=393

# Preface

To the best of my knowledge, this might be the first comprehensive, clinically oriented two-volume collection on the polypharmacy (co-administration of more than one medication) or the use of multiple preparations to treat psychotic, cognitive, mood and anxiety disorders. Despite the large number of psychotropic medications currently available, effective management of mental disorders continues to be a challenging task. Although monotherapy may be desirable, most patients require combinations of two or more psychotropic drugs. Polypharmacy aims to address different aspects of treatment resistance, especially insufficient response of positive and negative symptoms, cognitive disturbances, affective comorbidity, obsessive-compulsive syndromes and side-effects of antipsychotic agents. At the same time, evidence based guidelines in support of polypharmacy and augmentative strategies are scant.

This monograph is divided into four parts. Volume I contains two parts including chapters that serve as an introduction and overview of conceptual issues. Key topics include: a rational polypharmacy, receptor binding targets, drug interactions, preclinical and clinical investigation in this field, dosing regimens, multiple medication use in forensic psychiatry, a naturalistic trial, adjunctive strategies, and multiple medication use for the treatment of somatic symptom disorders.

Volume II contains two parts including chapters that focus on antipsychotic polypharmacy for schizophrenia; clinical practice in USA, Czech Republik, Ukraine, and Italy; polypharmacy and associated phenomena; clozapine combinations; and metabolic syndrome. The authors discuss combination therapy for bipolar disorder, major depressive disorder, obsessive-compulsive syndromes in schizophrenia, and potentially inappropriate medication use among elderly patients with dementia. Finally, each volume includes an Appendix that contains 'Annotated Bibliography on Polypharmacy' and 'List of Psychotropic Medications'.

Since many of the contributors to this collection are internationally known experts, they not only provide up-to-date state-of-the-art overviews, but also clarify some of the ongoing controversies and future challenges and propose new insights for future research. The contents of these volumes have been carefully planned,

organized, and edited. Of course, despite the assistance provided by the contributors, I alone remain responsible for the content of this monograph including any errors or omissions.

Editing this book has been an exciting journey that brought several incredible people into my life. First and foremost, I am grateful and thankful to all contributors for their excellent cooperation. I wish to thank the entire staff, heads of departments, and the medical director of the Shaar-Menashe Mental Health Center, Dr. Alexander Grinshpoon, M.D, MHA, Ph.D, for their commitment, and support. Thanks to Peter Butler and Dr. Martijn Roelandse, publishing editors, who did their utmost to promote this project. And of course, I would like to thank my lovely wife Stella for her tolerance of me having my head stuck in my computer. Without her love, patience and support I would not have completed this project.

I sincerely hope that this book will extend the knowledge in the complex field of treatment of psychiatric disorders and will be of interest to a broad spectrum of readers including psychiatrists, neurologists, neuroscientists, endocrinologists, pharmacologists, general practitioners, geriatricians, graduate students, and health care providers in the field of mental health.

Haifa Michael S. Ritsner
September, 2012

# Contents

# Contributors

**Peter F. Buckley M.D.** Department of Psychiatry and Health Behavior, Medical College of Georgia, Georgia Health Sciences University, Augusta, GA, USA

**André F. Carvalho, M.D., Ph.D.** Department of Clinical Medicine and Psychiatry Research Group, Faculty of Medicine, Federal University of Ceará, Fortaleza, CE, Brazil

**Tricia L. da Silva, M.A.** Mood and Anxiety Disorders Program, Centre for Addiction and Mental Health, Toronto, ON, Canada

**Luigi Ferrannini, M.D.** Department of Mental Health, ASL3 Genovese, Genoa, Italy

**Konstantinos N. Fountoulakis, M.D., Ph.D.** 3rd Department of Psychiatry, Division of Neurosciences, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

**Lucio Ghio, M.D.** Department of Neuroscience, Ophthalmology and Genetic, Psychiatry Section, University of Genoa, Genoa, Italy

**Xenia Gonda** Department of Clinical and Theoretical Mental Health, Faculty of Medicine, Semmelweis University, Budapest, Hungary

**Simona Gotelli, M.D.** Department of Neuroscience, Ophthalmology and Genetic, Psychiatry Section, University of Genoa, Genoa, Italy

**Heinz Grunze** Institute of Neuroscience, Academic Psychiatry, Campus of Aging and Vitality, Wolfson Research Centre, Newcastle University, Newcastle, UK

**Thomas N. Hyphantis, M.D., Ph.D.** Department of Psychiatry, Medical School, University of Ioaninna, Ioaninna, Greece

**Apostolos Iacovides** 3rd Department of Psychiatry School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

**Hiroto Ito** Department of Social Psychiatry, National Institute of Mental Health, Tokyo, Japan

**Rena Kurs, B.A.** Medical Library, Sha'ar Menashe Mental Health Center, Hadera, Israel

**Vladimir Lerner, M.D., Ph.D.** Ministry of Health, Faculty of Health Sciences, Ben Gurion University of the Negev and Be'er Sheva Mental Health Center, Be'er Sheva, Israel

**Jan Luzny, M.D.** Mental Hospital Kromeriz and Palacky University Olomouc, Praha, Czech Republic

**Danielle S. Macêdo, Ph.D.** Department of Physiology and Pharmacology, Faculty of Medicine, Federal University of Ceará, Fortaleza, CE, Brazil

**Stamatia Magiria** 3rd Department of Psychiatry, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

**Roger S. McIntyre, M.D., FRCPC** Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada

**Yong K. H. Michael, M.D., M.Med (Psychiatry)** Department of Psychological Medicine, Jurong Health Alexandra Hospital, Singapore, Singapore

**Masaru Mimura, M.D., Ph.D.** Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

**Chanoch Miodownik, M.D.** Ministry of Health, Faculty of Health Sciences, Ben Gurion University of the Negev and Be'er Sheva Mental Health Center, Be'er Sheva, Israel

**Fuminari Misawa** Yamanashi Prefectural KITA Hospital, Yamanashi, Japan

**Werner Natta, M.D.** Department of Neuroscience, Ophthalmology and Genetic, Psychiatry Section, University of Genoa, Genoa, Italy

**Yasuyuki Okumura** Department of Social Psychiatry, National Institute of Mental Health, Tokyo, Japan

**Anand K. Pandurangi, MBBS, M.D.** Division of Inpatient Psychiatry, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA

Schizophrenia Program and Brain Stimulation Therapies Program, Virginia Commonwealth University, Richmond, VA, USA

**Arun V. Ravindran, MBBS, M.Sc., Ph.D., FRCPC, FRCPsych.** Departments of Psychiatry, Psychology and Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada

Mood and Anxiety Disorders Program, Centre for Addiction and Mental Health, Toronto, ON, Canada

**Oksana E. Samokhvalova, M.D., Ph.D.** Department of Psychiatry, Central Military Hospital – Military University Hospital Prague, Prague, Czech Republic

**Viktor P. Samokhvalov, M.D., Ph.D., D.Sc.** Deutsch-Russische Gesellschaft für Psychiatrie, Psychotherapie und psychosoziale Gesundheit, Nürnberg, Germany

**Norman Sartorius, M.D., Ph.D.** Association for the Improvement of Mental Health Programmes, Geneva, Switzerland

**Frederike Schirmbeck, Dipl.-Psych** Department of Psychiatry and Psychotherapy, Medical Faculty Mannheim, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany

**Melina Siamouli** 3rd Department of Psychiatry, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

**Kang Sim, MBBS (Melb), M.Med (Psychiatry), PG Dip Psychotherapy (Distinction)** Institute of Mental Health (IMH), Singapore, Singapore

Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

**Takefumi Suzuki, M.D., Ph.D.** Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

Inokashira Hospital, Tokyo, Japan

**Hiroyuki Uchida, M.D., Ph.D.** Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

**Georgij N. Verbenko, M.D.** Department of Psychiatry, Crimean Medical University, Simferopol, Crimea, Ukraine

**Viktoria A. Verbenko, M.D., Ph.D.** Department of Psychiatry, Crimean Medical University, Simferopol, Crimea, Ukraine

**John T. Vernon, M.D.** Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA

**Koichiro Watanabe, M.D., Ph.D.** Department of Neuropsychiatry, Kyorin University School of Medicine, Tokyo, Japan

**Fujii Yasuo** Yamanashi Prefectural KITA Hospital, Yamanashi, Japan

**Mathias Zink, M.D.** Department of Psychiatry and Psychotherapy, Medical Faculty Mannheim, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany

# Part I
# Antipsychotic Polypharmacy

# Chapter 1
# Antipsychotic Polypharmacy in Schizophrenia: 'Secret Sauce or Wild Abandon?'

**Peter F. Buckley**

**Abstract** The treatment of schizophrenia has paradoxically become increasingly complex with the greater availability and choice among antipsychotic medications. At the same time, there is still substantial unmet need, as confirmed by recent large pragmatic trials in schizophrenia, which provides the therapeutic context for antipsychotic polypharmacy. For patients and clinicians, then, the question of "why and when do I combine medications?" is now very challenging. All available evidence suggests that antipsychotic polypharmacy is common in clinical practice. Additionally, it is a topic of enduring interest among clinicians who are always eager to understand the information contributing to key therapeutic strategies. This chapter will provide a current appraisal of the extant evidence-base that informs the daily decision making process that is the clinician's dilemma: how should I use antipsychotic polypharmacy to its best advantage in my practice? The chapter will also critically evaluate the extent to which polypharmacy truly impacts tolerability considerations in treating schizophrenia.

## Abbreviations

| | |
|---|---|
| AP | Antipsychotic polypharmacy |
| CATIE | Clinical Antipsychotic Trials of Intervention Effectiveness |
| EPS | Extrapyramidal side effects |
| FGA | First generation antipsychotic |
| NT | Neurotransmitters |
| PRN | Pro re nata |
| SGA | Second general antipsychotic |

P.F. Buckley, M.D. (✉)
Department of Psychiatry and Health Behavior, Medical College of Georgia, Georgia Health Sciences University, Augusta, GA, USA
e-mail: pbuckley@georgiahealth.edu

M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume II: Use of Polypharmacy in the "Real World"*, DOI 10.1007/978-94-007-5799-8_1,

## 1.1 Introduction

Few aspects, if any, of the psychopharmacology of schizophrenia draw more skepticism and negative attention than the practice of antipsychotic polypharmacy (AP). This is certainly not surprising, although perhaps the extent of clamor is disproportionate given the prevalence of AP – in the sense that most of us practice polypharmacy in some of our patients and yet we still decry the practice publically [1–3].

Although always a topic of intense interest, this is particularly so now as services curtail expenses on medications and also see to implement quality improvement process – AP has been a target in both circumstances [4–6]. Notwithstanding these considerations, the prevalence and extent of AP over time [7], in tandem with the 'one-off' accounts of great patient successes that we regularly hear from our astute clinician colleagues (vide infra), suggest that there is some merit – sometime, somehow, some circumstances – to this practice. While the latter argument may appear contrarian, more recent evidence is supportive of this commonplace practice. An influential meta-analysis [8] panning some 20 years of psychopharmacology reports a modest beneficial effect of AP. A more recent 6-month randomized trial with a comparable naturalistic follow-up period showed similar symptomatic outcomes between AP and antipsychotic monotherapy [9]. An accompanying editorial asks the question of the day *"When is polypharmacy an advantage?"* [2].

This chapter, appearing as one of many among a compendium solely dedicated to this vexing issue, will succinctly review the rationale(s) for AP. Since the topic of AP is given such comprehensive coverage in this book, an attempt is made in this chapter to minimize overlap with other contributions. To that end, aspects of prevalence and clinical impact of AP are well-covered in other chapters.

## 1.2 Why Do We Practice Antipsychotic Polypharmacy?

There are many and varied reasons why a clinician may resort to AP [10]. These are highlighted in Table 1.1 and are discussed further below. As described in other chapters, foremost among the reasons for AP is the failure of all our current antipsychotics to achieve the kind of superior therapeutic responses that our patients and we, as clinicians, expect. Lieberman and Stroup [11] provide a sobering account of the U.S. federal study CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) which, inter alia, showed overall comparability in outcomes across a broad range of drugs. Moreover, many patients discontinued medications altogether or moved on to the next phase of the study, thus displaying a high degree of customer dissatisfaction with current medications. It might be considered that the advent of second generation antipsychotics (SGAs) in long-acting injectable formulations might provide an added therapeutic advantage, thus lessening the need to resort to AP for either failed monotherapy and/or medication non-adherence. This does not appear to be the case and there is some data toward the opposite [12]. Thus, a sustained need exists and this continues to propel AP as a reasonable therapeutic

**Table 1.1** Rationale for antipsychotic polypharmacy in schizophrenia

| | |
|---|---|
| Pharmacodynamics | Targeting different receptors |
| | Boosting receptor blockade |
| | Use of different formulations in combination |
| | Prolong metabolism of primary agent |
| | Selective receptor target fine tuning agonist – antagonist effects |
| Efficacy-related | Boost overall response |
| | Target residual symptoms |
| | Target different symptoms |
| | Prevent relapse |
| | "Don't rock the boat" |
| | Sustained-suspended AP due to aborted switching ("Psychopharmacologic purgatory", P. Weiden, M.D.) |
| Tolerability-related | Permit dose reduction of primary antipsychotic |
| | Less side-effect burden |
| Administrative | 'Forensic' |
| | Practice service patterns |
| | Pharmaceutical marketing |

strategy. Moreover, it is plausible that the 'raising of the bar' by setting superior treatment expectations of recovery might engender continued AP.

### *1.2.1 Pharmacodynamic Considerations*

Clozapine, arguably one of the most effective antipsychotics available, has multiple effects on neuroreceptors. Although how it works is still not known, this pleiomorphic receptor profile is given strong consideration as a proposed mechanism of action. Bernardo and colleagues [12] report a low extent of AP in patients on clozapine. To the extent displayed by the receptor binding of the two (or sometimes three) antipsychotic drugs that a clinician might choose for AP, this approach could 'pharmacodynamically mimic' the profile of clozapine … and perhaps thereupon approximate toward its superior efficacy. It is perhaps noteworthy – in reverse argument – that when AP is studied by drug class, there is a trend for less AP among patients who are being treated with olanzapine [5, 13]. However, the converse argument that AP is disproportionately highest among the most neuroreceptor selective of antipsychotics does not appear to hold true [12]. Yet, there is still some rationale for use of AP to either target receptors that are relatively unaffected by the primary antipsychotic and/or to boost a small effect on important target receptor. For example, combining a first generation antipsychotic (FGA) with clozapine theoretically

augments the low dopamine (D2) binding that characterizes clozapine [14]. This might be advantageous – or it might disrupt clozapine's 'secret sauce'. Similarly, adding aripiprazole with its partial agonism could prove to be beneficial in providing 'soft touches' of additional D2 antagonism to other antipsychotics of differing D2 antagonism [15]. The same applies to a whole host of other combinations, be they FGA and SGA, SGA and FGA, or SGA and SGA, that might relate to dopamine as well as other receptors. This approach opens up various permutations. Along those lines, a glutamatergic antagonists without affinity for D2 receptors are being developed [16]. It is plausible that this approach might also be tried in AP.

There is also the instance of AP in relation to different formulations of antipsychotic medications. It is not uncommon in clinical practice to on a long-acting antipsychotic as well as an oral agent [12]. The oral agent may be the 'preferred' drug, with the long-acting drug also given to ensure medication adherence.

## 1.3 Efficacy-Related Reasons for Antipsychotic Polypharmacy

The rationale for pursuing AP to enhance overall efficacy has already been stated. This is also the reason given by experienced clinicians, as exemplified below:

> I have been in practice decades. I treat many schizophrenic patients. I think I try to correct their neurotransmitters (NTs) when not functioning properly. I use one med. It works for a while. Some symptoms return. This means the correction by one med has faded because of tolerance or because of NTs dysfunction occurring elsewhere and not being impacted by the one med (which has a limited number of NTs corrected). So I ADD ANOTHER med which will impact NTs other than the first med. The patient gets better and stays better. (That is a brief sample of my paradigm.) Of course it is more complicated than that but my experience is LOW DOSE COMBOS ARE BETTER THAN HIGH DOSE MONOS…and to stop meds because they fade effectiveness and relapse is to lose the benefit when you are half-way there when targeting the new or refractory symptoms by treating other NTs with a new med ADD-ON makes more sense and is more effective. I have reviewed all the combo studies and am unimpressed especially from my experience – in fact, I think they hint to what I have found. I think the resistance to "polypharmacy" is because the researchers cannot end up with statistically significant findings. Thus monotherapy is a Procrustean Bed!!! But the findings have welcome statistics – hooray! But my patients do not give a damn about that. If the meds are doing what they want and need, they will take them and get and stay better....such is the foxhole practice on the front lines – and it is LOW DOSE COMBOS ARE BETTER THAN HIGH DOSE MONOS. To think the involved NTs (how many are there?) can be corrected by one med is naive and unreasonable. (Sam Nigro, M.D., September 30, 2011)

Correll and colleagues [17] recently sampled the perceptions of doctors involved in AP. While those who preferred AP shared similar attitudes toward AP of those who used this strategy sparingly, they were likely to be of longer duration in clinical practice and to have a specific AP preference. This latter point is important because each clinician has his/her 'favorite' augmentation polypharmacy strategy and this differs between clinicians. Additionally, the present evidence-base for augmentation with AP does not preferentially endorse any individual agent and/or particular combination, thus until recently, AP strategies have not been scientifically unsubstantiated to any adequate extent [1]. This was in part due to the limited inferences from

**Table 1.2** The (predominant) use of naturalistic trials to study antipsychotic polypharmacy in schizophrenia

| Pros | Cons |
|---|---|
| Permits individualized treatments | Subject to multiple potential confounds |
| Results drive by clinician/patient choices | Lacks sufficient scientific rigor |
| Broad and representative patient populations | Difficult to interpret |
| Mirrors most closely clinical practice | Response often inadequately measured |
| Flexibility | Sample may have unappreciated local/site or physician biases |
| Does not attempt to control for other factors | Often small sample size (retrospective) studies |
| Can support large observational studies | Variable medication practices |
| Easier, less expensive, and quicker to conduct quantitative research | Cannot address rationale for AP |
| Resonates with clinician experiences | Multiple AP combinations exhaust methodological rigor to test each |

naturalistic studies – the predominant research methodology in studying AP (Table 1.2). However, Correll and colleagues [8] have synthesized all available literature in a comprehensive meta-analysis of 19 studies that were of superior methodology. In total, 1,229 patients were included in this meta-analysis. While the results were markedly heterogeneous, overall they reported a superior effect – number needed to treat of seven – favoring AP over antipsychotic monotherapy. They also found their result: clozapine AP, short trial duration, polypharmacy occurring simultaneously (hard to disentangle from switching medications), and SGA-FGA combinations. The study is of interest and, given the heterogeneity of included studies, its findings are surprisingly robust. However, the long duration of observation, as well as the inherent drawbacks of the meta-analytic strategy, should temper interpretations thereupon.

Essock and colleagues [9] report on a 6-month randomized trial of AP versus antipsychotic monotherapy. The trial was complicated by high rates of discontinuation early on in the switching phase. Nevertheless, during the 6-month follow-up the symptomatic outcomes were similar. The authors interpreted the clinical significance of their findings as supporting the rationale for transition from AP to monotherapy. That rationale was further buttressed by their finding of almost double the amount of weight gain among patients treated with AP.

The notion that AP can achieve selective benefits in discrete symptom domains is intuitive but still likely implausible [1, 10, 18]. For example, it has been observed that several SGAs have benefits in cognitive functioning and these appear to be different between agents. However, these individual effects on cognitive performance are so marginal that it seems implausible that combining two antipsychotics would result in any clinically meaningful improvement in cognition [19]. Similarly, the response of individual SGAs in treating negative symptoms of schizophrenia has been underwhelming [20]. It is unlikely here, too, that two is better than one. The evidence is not present.

On balance, then, the clinical rationale for AP results on improving symptoms overall and the evidence for this – aside from Correll meta-analysis – is (at best) inconclusive. The dilemma is, however, that group differences, or lack thereof, might obscure clinically meaningful individual differences. This is one of the lessons learned from CATIE [11]. It is also the rationale behind the decision making of astute clinicians (see above comments by Dr. Nigro).

## 1.4 Tolerability Considerations for Antipsychotic Polypharmacy

If anything, the rationale of adding two antipsychotics in an effort to reduce side-effects seems at first glance counter-intuitive. However, an elegant study by Fleishhacker and colleagues [21] is illustrative of the principle. This group sought to determine the merit of adding aripiprazole to clozapine. Clozapine is the most weight-inducing among all antipsychotics, while aripiprazole is characterized by a relatively low weight gain liability. In this study, adding aripiprazole allowed lower dose of clozapine with a concomitant reduction in weight in the group receiving both drugs. Henderson and colleagues [22] reported a similar effect when aripiprazole is added to olanzapine. Conversely, adding olanzapine to clozapine would seem injudicious as it could be 'doubling up' on the weight gain liabilities of both drugs. Similarly, adding haloperidol to risperidone risks greater extrapyramidal side effects (EPS) liability. On the other hand, adding haloperidol to quetiapine could potentially 'redistribute' the antipsychotic side effect burden between EPS and obesity rather than risk greater obesity at higher doses of quetiapine by monotherapy. Similar potential advantages exist for other SGA-SGA and SGA-FGA permutations, though FGA-FGA combinations appear sterile in this regard. Of course, such approaches are really predicated on the individual patient liabilities to each drug's side effects [3] and these are still highly variable for any given patient. The risk of these combinations is important to evaluate in each patient, especially since weight gain and metabolic liabilities might be cumulative and they would contribute more to long term morbidity and premature mortality [23]. In this regard, it is of interest to note that a recent pharmacovigilance study of all forms of polypharmacy found that the greatest long term risk of death was associated with concomitant use of benzodiazepines [24].

## 1.5 Administrative Considerations in Antipsychotic Polypharmacy

In the United States, at least, the service delivery model favors a 'don't rock the boat' treatment modality. Patients are seen monthly – or less frequently – for brief (15 min on average) medication checks. This practice pattern could predispose to AP, in that clinicians sensing that a patient is not doing well enough might resort to

adding 'a little something else' in favor of the more administratively demanding strategy of changing to a new antipsychotic. Additionally, there is substantial turnover of psychiatrists in the U.S. public mental health system, such that AP might be another preferred strategy which – once started – is sustained across successive treating psychiatrists.

There is also substantial PRN use of antipsychotics in U.S. inpatient units. Whether justified or not, antipsychotics are used as first-line treatments for aggressive behavior [25]. This is another practice pattern that is likely to facilitate AP.

It is also plausible that pharmaceutical marketing practices might contribute to AP. Indeed, antipsychotics have been used for a variety of non FDA-approved circumstances and this – combined with aggressive marketing strategies – could potentiate AP. While there is concern that U.S. psychiatrists are disproportionately vulnerable to conflicts of interest with pharmaceutical companies [26], there is no direct evidence that this has influenced AP in either direction.

## 1.6 Concluding Remarks

AP is difficult to study and thereupon difficult to draw conclusions about. Accordingly, this book should provide a very useful compendium of disparate information for clinicians. It remains a 'one patient at a time' event whose origins are poorly understood. In a revealing issue of *The American Journal of Psychiatry* that was largely dedicated to polypharmacy, an editorial [2] and accompanying commentary [3] both extol the need for selective research to clarify the rationale for AP and to determine whether AP is indeed some 'secret sauce' or 'wild abandon'.

## References

1. Stahl SM (2012) Antipsychotic polypharmacy: never say never, but never say always. Acta Psychiatr Scand 125(5):349–351
2. Tamminga CA (2011) When is polypharmacy an advantage? Am J Psychiatry 168(7):663
3. Goff DC, Dixon L (2011) Antipsychotic polypharmacy: are two ever better than one? Am J Psychiatry 168(7):667–669
4. Stahl SM, Grady MM (2006) High-cost use of second-generation antipsychotics under California's Medicaid program. Psychiatr Serv 57(1):127–129
5. Constantine RJ, Andel R, Tandon R (2010) Trends in adult antipsychotic polypharmacy: progress and challenges in Florida's Medicaid program. Community Ment Health J 46(6):523–530
6. Baandrup L, Allerup P, Lublin H, Nordentoft M, Peacock L, Glenthoj B (2010) Evaluation of a multifaceted intervention to limit excessive antipsychotic co-prescribing in schizophrenia outpatients. Acta Psychiatr Scand 122(5):367–374
7. Dussias P, Kalali AH, Citrome L (2010) Polypharmacy of schizophrenia. Psychiatry (Edgemont) 7(8):17–19
8. Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S (2009) Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized clinical trials. Schizophr Bull 35(2):443–457

9. Essock SM, Schooler NR, Stroup TS, McEvoy JP, Rojas I, Jackson C, Covell NH (2011) Effectiveness of switching from antipsychotic polypharmacy to monotherapy. Am J Psychiatry 168:702–708
10. Zink M, Englisch S, Meyer-Lindenberg A (2010) Polypharmacy in schizophrenia. Curr Opin Psychiatry 23(2):103–111
11. Lieberman JA, Stroup TS (2011) The NIMH-CATIE schizophrenia study: what did we learn? Am J Psychiatry 168(8):770–775
12. Bernardo M, Coma A, Ibañez C, Zara C, Bari JM, Serrano-Blanco A (2012) Antipsychotic polypharmacy in a regional health service: a population-based study. BMC Psychiatry 12(1):42
13. Procyshyn RM, Honer WG, Wu TK, Ko RW, McIsaac SA, Young AH, Johnson JL, Barr AM (2010) Persistent antipsychotic polypharmacy and excessive dosing in the community psychiatric treatment setting: a review of medication profiles in 435 Canadian outpatients. J Clin Psychiatry 71(5):566–573
14. Friedman JI, Lindenmayer JP, Alcantara F, Bowler S, Parak M, White L, Iskander A, Parrella M, Adler DN, Tsopelas ND, Tsai WY, Novakovic V, Harvey PD, Davis KL, Kaushik S (2011) Pimozide augmentation of clozapine inpatients with schizophrenia and schizoaffective disorder unresponsive to clozapine monotherapy. Neuropsychopharmacology 36(6):1289–1295
15. Kane JM, Correll CU, Goff DC, Kirkpatrick B, Marder SR, Vester-Blokland E, Sun W, Carson WH, Pikalov A, Assuncáo-Talbott S (2009) A multicenter, randomized, double-blind, placebo-controlled, 16-week study of adjunctive aripiprazole for schizophrenia or schizoaffective disorder inadequately treated with quetiapine or risperidone monotherapy. J Clin Psychiatry 70:1348–1357
16. Kantrowitz J, Javitt DC (2012) Glutamatergic transmission in schizophrenia: from basic research to clinical practice. Curr Opin Psychiatry 25(2):96–102
17. Correll CU, Shaikh L, Gallego JA, Nachbar J, Olshansky V, Kishimoto T, Kane JM (2011) Antipsychotic polypharmacy: a survey study of prescriber attitudes, knowledge and behavior. Schizophr Res 131(1–3):58–62
18. Shiloh R, Zemishlany Z, Aizenberg D, Radwan M, Schwartz B, Dorfman-Etrog P, Modai I, Khaikin M, Weizman A (1997) Sulpride augmentation in people with schizophrenia partially responsive to clozapine: a double-blind, placebo-controlled study. Br J Psychiatry 171:569–573
19. Goldberg TE, Keefe RS, Goldman RS, Robinson DG, Harvey PD (2010) Circumstances under which practice does not make perfect: a review of the practice effect literature in schizophrenia and its relevance to clinical treatment studies. Neuropsychopharmacology 35(5):1053–1062
20. Buckley PF, Stahl SM (2007) Pharmacological treatment of negative symptoms of schizophrenia: therapeutic opportunity or cul-de-sac? Acta Psychiatr Scand 115(2):93–100
21. Fleischhacker WW, Heikkinen ME, Olié JP, Landsberg W, Dewaele P, McQuade RD, Loze JY, Hennicken D, Kerselaers W (2010) Effects of adjunctive treatment with aripiprazole on body weight and clinical efficacy in schizophrenia patients treated with clozapine: a randomized, double-blind, placebo-controlled trial. Int J Neuropsychopharmacol 13(8):1115–1125
22. Henderson DC, Fan X, Copeland PM, Sharma B, Borba CP, Boxill R, Freudenreich O, Cather C, Evins AE, Goff DC (2009) Aripiprazole added to overweight and obese olanzapine-treated schizophrenia patients. J Clin Psychopharmacol 29:165–169
23. Baandrup L, Gasse C, Jensen VD, Glenthoj BY, Nordentoft M, Lublin H, Fink-Jensen A, Lindhardt A, Mortensen PB (2010) Antipsychotic polypharmacy and risk of death from natural causes in patients with schizophrenia: a population-based nested case–control study. J Clin Psychiatry 71:103–108
24. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P (2012) Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Arch Gen Psychiatry 69(5):476–483
25. Buckley PF, Miller BJ, Lehrer DS, Castle DJ (2009) Psychiatric comorbidities and schizophrenia. Schizophr Bull 35(2):393–402
26. Insel TR (2010) Psychiatrists' relationships with pharmaceutical companies: part of the problem or part of the solution? JAMA 303(12):1192–1193

# Chapter 2
# Antipsychotic Polypharmacy in USA

**Anand K. Pandurangi and John T. Vernon**

**Abstract** Fifty-six million prescriptions were dispensed for antipsychotics in the USA in 2010, at an estimated cost of $16.1 billion, and 90% of these were for atypical antipsychotics (IMS Institute for Healthcare Informatics: The use of medicines in the United States: review of 2010). Co-prescription of two (or more) antipsychotics or so-called polypharmacy is estimated from 2 to >50% depending on the population surveyed. Antipsychotic polypharmacy is of considerable importance from multiple perspectives such as its sheer volume, quality and safety of care, and cost. There is much variability in this practice based on age group, primary and co-morbid diagnoses, practice setting, health insurance status, etc. A thorough understanding of the associated factors is necessary to know what drives and maintains polypharmacy practice

Psychiatric, pharmacological and systems-of-care factors separately or together influence physician co-prescribing of two or more antipsychotics. Psychiatric factors include partial response to monotherapy, co-morbid psychiatric syndromes including behavioral challenges, and adverse effects or intolerance of high dose monotherapy, including but not limited to extra-pyramidal symptoms, metabolic effects and sedation. Pharmacological factors include variable receptor effects and pharmacokinetics. The third set of factors that sustains polypharmacy include the need to produce rapid clinical response, pressures of managed care, patient preferences and family concerns about specific symptoms and behaviors, the cross-titration trap, and the need to obtain treatment adherence.

A.K. Pandurangi, M.B.B.S., M.D. (✉)
Department of Psychiatry, Virginia Commonwealth University, P.O. Box 980710, Richmond, VA 23298, USA

Schizophrenia Program and Brain Stimulation Therapies Program, Richmond, VA, USA
e-mail: apandurangi@mcvh-vcu.edu

J.T. Vernon, M.D.
Department of Psychiatry, Virginia Commonwealth University, P.O. Box 980710, Richmond, VA 23298, USA

M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume II: Use of Polypharmacy in the "Real World"*, DOI 10.1007/978-94-007-5799-8_2,

This chapter describes the scope of antipsychotic polypharmacy in the USA in different clinical settings, and why clinicians find it necessary to prescribe multiple antipsychotics. We review the clinical and research evidence for and against antipsychotic polypharmacy and its practice in USA, and discuss the challenges confronting the patient, clinician, healthcare managers and policy makers. Cost of polypharmacy and interventional studies to change or reduce the practice of polypharmacy are also reviewed.

Antipsychotic polypharmacy will likely persist due to clinical necessity. Rather than pursue prescriptive, prohibitive, and/or regulatory approaches to complex patient management, it may be pragmatic to develop rational and cost-effective polypharmacy guidelines, and encourage translational research that will assist clinicians in cost-effective, evidence-based practices while meeting the unique needs of their patients.

## Abbreviations

| | |
|---|---|
| AAP | Atypical Antipsychotic |
| AP | Antipsychotic |
| APM | Antipsychotic Monotherapy |
| APP | Antipsychotic Polypharmacy |

## 2.1 Introduction

Antipsychotic polypharmacy (APP) is a common practice around the world. In the USA such polypharmacy rates have been found to be around 2–7% in general medical practices, around 15% in outpatient psychiatric settings, between 20 and 30% in schizophrenia patients, and >50% in the long term course of treatment for patients with schizophrenia [2–7]. There is much variability in these rates. Whereas data captured by cross sectional studies in large populations of patients counting co-prescriptions at any one point in time reveal APP in the 10–25% range, studies that examine how patients fare over a longitudinal course of treatment such as 1- or 2-years, indicate that 30–50% of patients receive APP at some point in this course. APP is by no means a novel phenomenon. In 1974, Sheppard and Beyel [8] surveyed psychiatrists in New York, Pennsylvania, California, and Texas and found APP was prevalent, and sometimes combinations of up to six neuroleptics were used! Chlorpromazine-trifluperazine was the most common combination.

The practice of APP has sustained despite the fact that various guidelines for the treatment of Schizophrenia, and literature reviews of the evidence for and against APP generally suggest that it should be a practice of last resort [9, 10]. The most

significant factor sustaining APP appears to be the fact that antipsychotic monotherapy (APM) for schizophrenia has significant limitations [3, 11]. Treatment nonresponse with monotherapies is estimated at up to 30%. American Psychiatric Association (APA) practice guidelines from 2004 acknowledge that an additional 30% of patients have only partial response to APM [10]. In this context, APP is by no means universally dismissed in the available literature. Polypharmacy is an accepted practice in the treatment of chronic, complex and multifactorial disorders such as hypertension, diabetes, epilepsy, etc [12]. Nor does APP inherently lead to increased adverse effect burden. The latter is determined by the specific drugs and doses [13]. The idea of rational APP has been put forward. Preskorn and Lacey [14] describe criteria for so-called rational co-pharmacy to include the following: evidence for benefit from combination therapy, evidence for improved efficacy over monotherapy, equal or improved safety/tolerability compared to monotherapy, pharmacokinetic/dynamic simplicity and minimal interactions, and combination of drugs that do not antagonize each other or have completely overlapping mechanisms of action. Used in an informed pharmacologic/pharmacokinetic fashion, there may very well be benefits [4, 15]. However as Stahl [16] has observed such benefits are not established in well controlled trials, and unlike polypharmacy in other medical disorders, it is not necessarily proved that the different receptor-binding profiles of antipsychotic medications represent sufficiently distinct mechanisms of action. Finally, in judging the appropriateness of APP, one has to keep in mind not just the diagnostic indication or similarity in efficacy of the drugs being used, as the determining factors but also quality of daily life.

Thus any review of APP and the state-of-the-art needs to consider the limitations of APM, potential benefits and side effects, evidence for and against APP, realities of clinical practice, and cost – benefit of APP in a comprehensive and balanced manner.

## 2.2 Prevalence of APP in the USA

There are numerous estimates of the practice of APP throughout the world. In the United States, APP for patients with Schizophrenia is around 17% with a range between 10 and 30% in most studies. In comparison, APP was estimated at somewhat higher rates in other countries, 30% in the United Kingdom, 46–90% in East Asian countries, 25% in Spanish community practice and 45% in Spain's hospitals [17]. However, prevalence rates of APP in the USA vary from a low of 3% to as much as 55% and this range is too wide to be of much use. Understandably APP rates in general medical ambulatory practices are low and range between 0.04% to about 3.7% [18, 19], while in psychiatry settings, the rates range from 7% in closely monitored systems such as the Veterans Administration, between 20 and 30% in community hospitals and practices, and >50% in long term facilities [2–7, 20, 21] (Table 2.1).