Michael S. Ritsner *Editor*

Polypharmacy in Psychiatry Practice

Volume I

Multiple Medication Use Strategies

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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, M.D., Ph.D. 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, MD, MHA, PhD, 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

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Part I
Polypharmacy Treatment Strategies

Chapter 1
Multiple Psychiatric Medications Use in Psychiatry: How Rational Can It Be?

Ahsan Y. Khan and Sheldon H. Preskorn

Abstract The focus of this chapter is to discuss how rational it can be to use multiple psychiatric medications in combinations to treat an individual patient and what are the basic principles to follow when doing so. This matter is put in the context of the rest of medicine where multiple medication use (MMU) can be based on a highly sophisticated rationale based on knowledge of the pathoetiology and pathophysiology of the illness being treated (e.g., Human Immuno Deficiency Virus- HIV) to a less sophisticated rationale because of limited understanding of the nature of the illness (e.g., bipolar disorder). In this regard, all diagnoses in medicine including psychiatry can be grouped into four hierarchical levels of understanding ranging from least sophisticated (symptomatic diagnoses) to the most sophisticated where pathoetiology and pathophysiology are known. Parenthetically, the goal of medicine as a field is to achieve the highest level of diagnostic sophistication possible to improve their ability to treat or alter the course of the disease. Unfortunately, most psychiatric diagnoses are still at the syndromic level and hence psychiatric medications are typically aimed at the alleviation of sign and symptoms of these disorders. Moreover, two related phenomena are increasing the frequency and complexity of MMU in psychiatry. The first is the increase in the number and types of psychiatric medications available: Since 1990, the Food and Drug Administration (FDA) approved almost 40 new psychotropic drugs to treat a variety of psychiatric illnesses. Second, the ability to rationally designed psychopharmaceuticals has further increase the potential, perhaps

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the need and perhaps the rationale behind psychiatric MMU. Nevertheless, until knowledge of the pathoetiology and pathophysiology of psychiatric diagnoses progresses beyond the syndromic level, the rationale underlying psychiatric MMU will remain more limited than is ideal.

Keywords Multiple psychiatric medication use • Rational therapeutics • Diagnostic hierarchy • Pharmacokinetics • Rationale for multiple medication use

Abbreviations

AIDS	Acquired Immuno Deficiency Syndrome
APA	American Psychiatric Association
CO-MED	Combining Medications to Enhance Depression Outcomes
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision
EPS	Extra Pyramidal Symptoms
HIV	Human Immuno Deficiency Virus
MMU	Multiple Medication Use
MPMU	Multiple Psychiatric Medications Use
QIDS-SR	Quick Inventory of Depressive Symptomatology-Self Report
SSRI	Selective Serotonin Reuptake Inhibitors
STAR*D	Sequence Treatment Alternatives to Relieve Depression
WHO	World Health Organization

1.1 Introduction

> In diseases of the mind … it is an art of no little importance to administer medicines properly; but, it is an art of much greater importance and more difficult acquisition to know when to suspend or altogether to omit them [1]
>
> —Philippe Pinel

The above quote by Philippe Pinel illustrates the need for knowledge, skills and a philosophy to guide the clinician when prescribing multiple medications.

The World Health Organization (WHO) conference of 1985 in Nairobi, Kenya stated:

> Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own requirements, for an adequate period of time, and at the lowest cost to them and their community [2].

In this chapter, the authors first discuss the common reasons for multiple medication use (MMU) & Multiple Psychiatric Medications Use (MPMU). They discuss how new drug development in the last three decades paved the way for MPMU in present day practice of psychiatry. The authors then present the rationale for MMU

Table 1.1 Types of MMU

Type	Definition
1. Total MMU/All MMU	All drugs regardless of therapeutic indication(s) or mechanism of action
2. CNS Active MMU	Only drugs which affect the brain are considered but may not have a FDA approved CNS indication (e.g. beta blockers)
3. CNS Indication MMU	Only drugs which have a FDA approved CNS indication but not necessarily a FDA approved psychiatric indication are considered (e.g. phenytoin)
4. Psychiatric Indication MMU	Only drugs which have a FDA approved psychiatric indication are considered

using dimensional approach which goes from diseases and treatment for which much is known about their pathoetiology and pathophysiology (e.g., Human Immuno Deficiency Virus- HIV) to ones for which much less is known (e.g., most psychiatric illnesses). Finally, authors list principles to guide clinicians about rational MPMU and explain each principle in detail with examples drawn from psychiatric practice.

Traditionally, MMU has been termed "polypharmacy" which has a negative connotation, implying an inappropriate or excessive and perhaps even an irrational use of medications. The authors prefers MMU over polypharmacy because it is less judgmental and because MMU can be highly rational and appropriate depending on how much is known about the nature of the illness and its treatment. MMU is a broad term which includes the use of medications from different therapeutic classes and with different mechanisms of actions. It is beyond the scope of this chapter to cover the topic of MMU completely. MMU can be divided into four different types as outlined in Table 1.1.

1. ***Total/All MMU*** occurs when drugs are used in combination regardless of their therapeutic class, FDA indication or mechanism of action. For example, patients with HIV are not only treated with antiretroviral medications, but are also on medications needed to treat adverse effects from antiretroviral drugs, to treat co-morbid medical conditions with HIV, and to treat co-morbid psychiatric conditions with the disease as well.
2. Second category is Central Nervous System (***CNS) active MMU***: This category includes those medications which can affect brain receptors, chemicals and structures but are not Food and Drug Administration (FDA) approved to treat any specific CNS disorder. For example, pindolol, a beta blocker indicated for heart diseases but can affect brain and can be used as an augmentation option with antidepressants to treat depression. None of the beta blockers have a FDA approved CNS indication.
3. Third type is ***MMU with CNS indications***: This includes those medications which have FDA approved CNS indications but are not FDA approved to treat any psychiatric disorders. However, these medications can affect/treat psychiatric conditions. For example, anticonvulsants like valproate, lamotrigine and extended release formulation of carbamazepine, are FDA approved to treat bipolar disorder

Table 1.2 Questions psychiatrist must be able to answer before MPMU

• Can psychotherapy not address residual or refractory symptoms?
• Why am I using more than one drug to treat a single disorder?
• Is another drug really needed?
• Do the drugs interact?
• If so, what are the data supporting the safety, tolerability, and efficacy of the combination?
• Is this time to revisit the diagnosis?
• Are the co-morbid psychiatric conditions put the patient at special risk for MPMU?
• Can the patient afford to take multiple medications?
• How will MPMU affect overall compliance?
• Does the patient stand to gain more from adding a medication than removing one or lowering the dose?

but other anticonvulsants like topiramate, oxycarbamazepine, and immediate release carbamazepine are in use to treat bipolar disorder but have no FDA labeled indication instead such use may be based on research studies, case reports or series, and/or expert opinion.

4. Last category is ***MMU with psychiatric medications***: This includes MPMU to treat a specific psychiatric condition e.g., combination of FDA approved psychiatric medications to treat bipolar disorder and at time treatment resistant depression. Such combinations may or may not have a FDA labeled indication such as aripiprazole augmentation of a Selective Serotonin Reuptake Inhibitor (SSRI) (labeled) versus mirtazapine to augment venlafaxine (not labeled).

This last category is the main focus of this chapter which will discuss how rational it can be to use multiple psychiatric medications in combinations to treat an individual patient, and what are the basic principles to follow when doing this practice. However, the rational use of multiple medications in general is not an all or none phenomenon, rather it is dimensional. No definition of rational use of multiple medication was found in the literature, but in general, rational use of multiple medications means prescribing drug combinations to maximize the chances of efficacy and at the same time minimize medication induced adverse effects. Based on this dimensional concept, the authors propose the following definition for rational use of multiple medications;

> Rational use of multiple medications is a broad term ranging from completely random use of multiple medications with no logic or rationale to highly rational based on a firm understanding of the pathoetiology and pathophysiology of the illness and how the various drugs interact to affect that pathoetiology or pathophysiology in an effective and safe manner.

Next the authors will discuss what could be the reasons behind MMU and MPMU.

For MMU, the rationale of combining medications may be to produce a pharmacodynamic interaction in which the effect of one drug accentuates or diminishes the effect of another. Alternatively, the rationale could also be to produce a pharmacokinetic interaction in which one drug alters the absorption, distribution, metabolism, or elimination of another drug. For MMU to be rational, the treating psychiatrist must be able to answer several questions as outlined in Table 1.2.

Another reason for MMU is that the treatment over the last several decades has moved from a focus on time-limited therapy (i.e., a few weeks) of an acute illness (e.g., antibiotics for an acute infection) to preventive or maintenance therapy for chronic illnesses as diverse as major depressive disorder (MDD), schizophrenia, Alzheimer's disease, hypertension, HIV, and dyslipidemia. For this reason, patients are much more likely to be on more than one medication at the same time [3–5]. So in reality, MMU is the rule rather than exception in modern medicine.

In general practice of medicine, patients being treated with a psychiatric condition are more likely than patients not on a psychiatric medication to be on MMU and more complex MMU. Silkey et al. reported that psychiatric patients tend to be receiving more medications than age-matched non-psychiatric patients, and have been associated with an increased risk of inappropriate prescribing [6]. Goldman reported that patients with psychiatric disorders have significant co-morbidity with medical conditions. Some of these co-morbid conditions result from or are aggravated by effects of psychiatric medications [7]. For example, new onset diabetes mellitus, hyperlipidemia, obesity and hypertension are all common side effects associated with use of atypical antipsychotics and their development may lead to treatment resulting in MMU. Colley et al. reported that psychotropic medications may also results in worsening or emerging psychiatric symptoms such as anxiety, Extra Pyramidal Symptoms (EPS), insomnia, psychosis and treating those side effects may also result in MMU in those patients [8].

On the other hand, MPMU could be the result of the recent approach to modern drug development (i.e., rationally designed psychopharmaceuticals) and may make MPMU even more necessary than it has been in the past. Preskorn et al. reported that one goal of rational drug development is to produce new drugs with limited numbers of mechanisms of action that will have a wider therapeutic index and be better tolerated (i.e., both fewer overall numbers and fewer types of adverse effects) while either maintaining or improving efficacy [9]. However, because of their reduced range of central nervous system effects, such drugs may have more limited clinical applications as single agents. This fact, coupled with the reduced risk of pharmacodynamic interactions when combining drugs with fewer mechanisms of action, sets the stage for more rational drug combination strategies in psychiatry.

Another major reason for MPMU is increase in number of psychiatric medications approved by FDA. Since 1990, the FDA approved almost 40 new psychotropic drugs to treat a variety of psychiatric disorders as shown in Table 1.3 [10].

Another common reason for MPMU is the syndromic nature of the common psychiatric disorders. They usually have multiple signs and symptoms, and therefore treatment aimed at specific symptoms (e.g., insomnia or restlessness) may lead to MPMU. Nichol et al. found that patients diagnosed with mania have been found to be four times more likely to receive multiple psychotropic medications, and those diagnosed with Schizophrenia were three times more likely [11]. Their symptom clusters wax and wane over the course of illness leading to MPMU.

Underutilization of social and behavioral techniques in modern psychiatry practice is a common reason for MPMU. Mintz et al. found decreased utilization of behavioral and social techniques for psychiatric symptoms, even by psychiatrists.

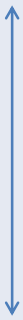
Table 1.3 Psychotropic medications approved since 1991

#s	Approval year	Generic name	Brand name
1	1991	Sertraline	Zoloft
2	1992	Paroxetine	Paxil
3	1992	Zolpidem	Ambien
4	1993	Venlafaxine	Effexor
5	1993	Risperidone	Risperidol
6	1994	Nefazodone	Serzone
7	1996	Mirtazapine	Remeron
8	1996	Olanzapine	Zyprexa
9	1996	Donepezil	Aricept
10	1997	Quetiapine	Seroquel
11	1998	Modafinil	Provigil
12	1998	Citalopram	Celexa
13	1999	Zaleplon	Sonata
14	2000	Rivastigmine	Exelon
15	2001	Ziprasidone	Geodon
16	2002	Aripiprazole	Abilify
17	2002	Escitalopram	Lexapro
18	2002	Atomoxetine	Strattera
19	2003	Memantine	Namenda
20	2003	Lamotrigine	Lamictal
21	2003	Olanzapine and Fluoxetine	Symbyax
22	2004	Duloxetine	Cymbalta
23	2004	Carbamazepine	Equetro
24	2004	Eszopiclone	Lunesta
25	2004	Galantamine	Razadyne (formerly Reminyl)
26	2005	Ramelteon	Rozerem
27	2006	Emsam	Selegiline
28	2006	Paliperidone	Invega
29	2006	Varenicline	Chantix
30	2007	Lisddexamfetamine	Vyvanse
31	2009	Iloperidone	Fanapt
32	2009	Asenapine	Saphris
33	2009	Guanfacine	Intuniv
34	2009	Clonidine XR	Kapvay
35	2010	Lurasidone	Latuda
36	2010	Doxepin	Silenor
37	2010	Trazodone XR	Oleptro
38	2011	Vilazodone	Viibryd

For example, encouragement of proper sleep hygiene in patients complaining of insomnia instead of prescribing sedative/hypnotics and a reluctance to take them off of those medications later can lead to MPMU [12].

A commonly used strategy in psychiatry is to boost or augment the efficacy of the primary treatment by combining it with another drug. For example, combining a

Table 1.4 A dimensional view of rational multiple medication use (MMU)

	Example	Rationale
Highly evolved and substantially evidence based rationale for MMU	HIV combined treatment	Pathoetiology known. Each drug aimed at that Pathoetiology. Substantial evidence of efficacy, safety, & tolerability.
	Cancer	Pathoetiology known in part. Pathophysiology known. Each drug aimed at either Pathoetiology and/or Pathophysiology. Substantial evidence of efficiency outweighing safety & tolerability concerns.
	Parkinson's disease	Pathoetiology unknown. Pathophysiology and biochemistry known. Each drug aimed at pathophysiology. Substantial evidence of efficacy outweighing safety & tolerability concerns.
Not as evolved and/or not as evidence based rationale for MMU	Bipolar disorder or Major depression	Pathoetiology unknown. Pathophysiology understanding limited. Drugs are aimed at signs and symptoms. Evidence of efficacy outweighing safety or tolerability concerns is limited.

SSRI and bupropion to treat a patient with major depressive disorder will necessarily will qualify as MPMU.

Next the authors will discuss the different levels of diagnostic hierarchy and then will present a dimensional view of how to do rational MMU in treating patients with HIV, cancer and Parkinson's disease (Table 1.4).

To explain this aspect of MMU, it is important to understand the hierarchy of diagnostic sophistication and how it is associated with MMU and MPMU. In general, drugs are developed to treat a specific diagnosis. That is the usual requirement for drug approval by regulatory bodies such as the FDA. Response to a specific drug is dependent on having a specific diagnosis that is responsive to drug's mechanism of action. On the other hand, all diagnoses can be grouped into four hierarchical levels of diagnostic sophistication as illustrated in Fig. 1.1 [13]. The least sophisticated level is symptomatic diagnoses (e.g., headache or psychosis). Syndromic diagnoses are at the next level and are based on the observation that a group of patients are presenting with the same cluster of symptoms and signs, suggesting a

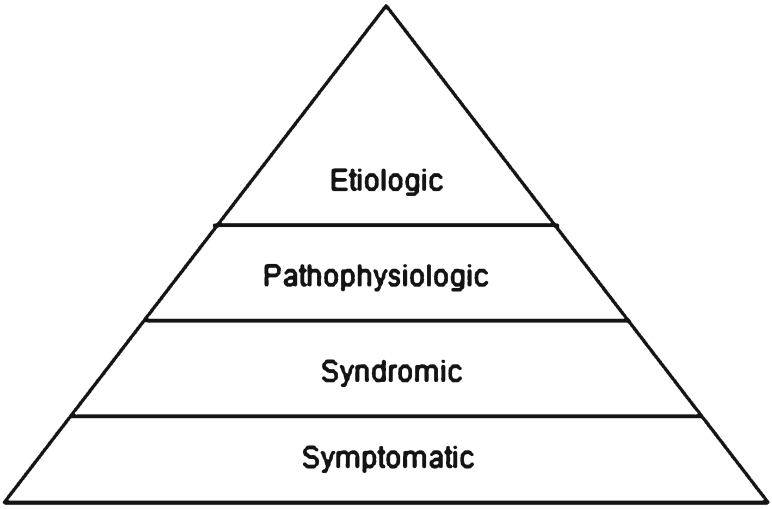


Fig. 1.1 Diagnostic criteria pyramid (Reproduced with permission from S. Preskorn)

common disease process (e.g., rheumatoid arthritis or psychiatric condition). The next level is diagnosis based on pathophysiology which is based on documented biological and physical manifestations which correlate with the stage and/or severity of the illness (e.g., Parkinson's disease). Pathophysiology does not deal directly with the treatment of disease, rather, it explains the processes within the body that result in the signs and symptoms of a disease. Finally, the highest level of diagnostic sophistication is where both pathophysiology and pathoetiology of the disease are known (e.g., infection with HIV). It was first a syndrome without a known pathophysiology or pathoetiology but has now progressed to an etiologic diagnosis (HIV infection) and treatment is aimed at blocking the development of the terminal syndrome (i.e., Acquired Immuno Deficiency Syndrome- AIDS). The goal of the clinician and the researcher is to achieve the highest level of diagnostic sophistication possible i.e., at the pathophysiology and pathoetiologic level to improve their ability to alter the course of the disease process.

Based on this concept of diagnostic sophistication, MMU can be divided into highly evolved and substantially evidence based such as HIV combined treatment, to less evolved and/or less evidence based such as bipolar disorder treatment (Table 1.4).

1.2 Rationale for MMU in HIV

Soon after the identification of AIDS, flood gates opened for research which first led to an improved understanding of the pathophysiology underlying the syndrome—a progressive loss of specific types of lymphocytes and then to an understanding of the

pathoetiology—infection with HIV. Understanding the pathophysiology and pathoetiology are the final two levels of diagnostic sophistication. The identification of HIV as the causative agent in AIDS introduced the development of practices that reduce the risk of acquiring the virus and if already acquired, to the development of drugs that arrest the progression of the disease process thus preventing or delaying the development of AIDS.

Even though there is no cure for HIV/AIDS, multiple medications can be used in combination to control viral replication. Each of the classes of anti-HIV medications blocks the virus in a different way. Gulick et al. reported that there is scientific evidence that suggests combining at least three drugs from two different classes [**non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), entry or fusion inhibitors (E/FIs), and integrase inhibitors (IIs)**] avoids creating strains of HIV that are immune to a single drug [14]. Each antiretroviral drug aimed at the pathoetiology and pathophysiology of HIV as outlined below.

- NNRTIs disable a protein needed by HIV to make copies of it-self e.g., efavirenz (Sustiva)
- NRTIs are faulty versions of building blocks that HIV needs to make copies of itself e.g., zidovudine (Combvir)
- PIs disable protease, another protein that HIV needs to make copies of itself e.g., ritonavir (Norvir)
- E/FIs blocks HIV entry into CD4 cells e.g., enfuvirtide (Fuzeon)
- IIs works by disabling integrase, a protein that HIV uses to insert its genetic material into CD4 cells e.g., raltegravir (Isentress)

The rationale to use multiple medications in HIV is based on the fact that HIV/AIDS needed a therapy based on simultaneous delivery of a cocktail of drugs, because of the virus' capacity for rapid evolution. Substantial evidence of efficacy, safety and tolerability exist for HIV drug combinations.

1.3 Rationale for MMU in Cancer

Based on our knowledge of pathophysiology and pathoetiology of cancer, it is a disease of cells gone awry, of uncontrolled proliferation, of the loss of normal patterns of cell behavior. Cancer arises from a series of genetic and epigenetic changes (usually DNA-associated proteins that influence gene expression) that endow the cancer cell with its malignant behavior. Researchers study cancer-related mechanisms of DNA damage and repair, and investigate tumor immunology, as well as other responses of the body to cancer, and the biology of malignancies of the immune system.

Researchers have used drugs combinations since the earliest days of cancer therapy. Each drug aims at either pathoetiology and/or pathophysiology of the cancer. As in HIV/AIDS, successful cancer treatments have evolved empirically using a cocktail of low specificity and highly toxic drugs. Modern cancer drugs are

Table 1.5 Parkinson's disease as a model of rational copharmacy

Treatment	Effect
L-Dopa	Increase synthesis of central dopamine (type: pk)
L-Dopa plus carbidopa (Sinemet)	Inhibit peripheral decarboxylase to reduce the dose of L-Dopa needed to increase synthesis of central dopamine (type: pk)
L-Dopa/carbidopa plus dopamine reuptake inhibitor (e.g., bupropion, amantadine)	Potentiate the effect of released central dopamine (type: pk)
L-Dopa/carbidopa plus L-deprenyl	Increase synthesis of central dopamine and block its degradation (type: pk)
L-Dopa/carbidopa plus a bromocriptine	Potentiate central dopamine agonism by addition of direct dopamine agonist (type: pd)

Type refers to type of interaction: *pk* pharmacokinetie; *pd* pharmacodynamic

often developed to hit specific targets within cancer cell. But when using a drug that attacks a single target, the disease often develops resistance to the treatment and comes back in a more aggressive form. Attacking with multiple drugs from the beginning may be able to prevent that process. Substantial evidence of efficacy outweighing safety and tolerability concerns exist.

Next disease in diagnostic hierarchy using dimensional approach for rational MMU is Parkinson's disease.

1.4 Rationale for MMU in Parkinson's Disease

In Parkinson's disease the pathophysiology and biochemistry is known but the pathoetiologic mechanism responsible for initiating nigral cell death remains elusive. Multiple mechanisms have been implicated, including oxidant stress, excitotoxicity, mitochondrial dysfunction, and proteosomal dysfunction. However, most researches would agree that nigral degeneration is most likely due to the cumulative effect of multiple processes such as age—related changes, genetic constitution, and toxin (endogenous or exogenous) exposure predispose individuals to nigral degeneration. Nigral degeneration results in dopamine deficiency, therefore the goal of treatment is to increase central dopamine activity.

It is rare to use a single drug to treat Parkinson's disease (Table 1.5). The cornerstone of treatment is a combination of L-dopa (L-3,4-dihydroxyphenylalanine) and carbidopa (Sinemet) [15]. At least early in the course of the disease, promoting dopamine in the nigrostriatal pathway can be accomplished by supplying the substrate, L-dopa, which is then decarboxylated to dopamine. However, this reaction can occur in the periphery as well as centrally. Dopamine cannot cross the blood-brain barrier. Hence, the conversion in the periphery decreases the effective dose of L-dopa available to reach the target organ (i.e., the brain) [16]. Although increasing the dose of L-dopa can overcome this problem, it may also result in an increased incidence of peripheral adverse effects caused by excessive peripheral dopamine agonism. For this reason,

carbidopa was added to L-dopa to inhibit dopa decarboxylase activity in the periphery and thus increase the bioavailability of the administered L-dopa to the brain. Several other ways to rationally augment the central action of L-dopa are shown in Table 1.5.

It was possible to develop such rational drug combination and even multiple medication model for Parkinson's disease because the pathophysiology of this condition is relatively simple and understood. The dysfunction in Parkinson's disease involves a single neurotransmitter. The neuroanatomy and neurophysiology have been elucidated, can be readily studied, and pharmacologically manipulated [17].

The treatment of Parkinson's disease may also provide a model for understanding a frequently troubling and perplexing phenomenon: many clinicians report that antidepressants, particularly SSRIs, seem to lose their effectiveness over time in a substantial number of patients. Although L-dopa can be a miracle drug early in the treatment of Parkinson's disease, it predictably loses its effectiveness during long-term treatment. The reason is based on the pharmacology of the drug versus the nature of the illness: L-dopa temporarily ameliorates the pathophysiology but does not correct the pathoetiology that results in the loss of central dopamine neurons. As these neurons die, L-dopa can no longer be converted to dopamine and thus it loses its efficacy. At least in some patients, antidepressants may simply correct the pathophysiology of a condition that is pathoetiologically progressive. If so, such drugs will predictably lose their efficacy over time.

Rationale for MPMU in psychiatric disorders is not as evolved and sophisticated as for HIV, some forms of cancer, and Parkinson's disease because knowledge of the pathoetiology and pathophysiology of psychiatric disorders is not as advanced as is the case in the other illnesses. Majority of the psychiatric diagnoses are at the syndromic level and these syndromes are the basis by which patients are grouped into "disease" clusters and are codified in the United States in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) of the American Psychiatric Association [18]. The overlap in symptoms and signs in psychiatric syndromes as currently defined in DSM-IV-TR may have produced some blurring of the diagnostic boundaries, creating high rates of "comorbid" psychiatric diagnosis and thus leading to the apparent increase in the practice of MPMU in psychiatry.

Next, the authors are going to present several principles and the rationale to guide clinicians for MPMU to treat psychiatric conditions. The authors discuss both validated and empirical strategies of MPMU and recommend that validated strategies, when they exist, be tried before other strategies if mono-therapy in adequate doses for an adequate duration has failed.

1.5 The Principles and the Rationale for MPMU

Principles and rationale for MPMU as outlined in Table 1.6.

1. ***Scientific evidence that the combination is more effective than mono-drug therapy.*** The basis for using a drug combination is based on reliable data from formal studies comparing the efficacy and safety of different combinations in