



## Complex psychotropic polypharmacy among patients with bipolar disorder

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### Abstract:

Psychotropic polypharmacy, which is the use of two or more psychotropic drugs in the same patient could be simple or complex depending on the number of psychotropic drugs prescribed. In clinical psychiatry, a common practice of polypharmacy is observed. As polypharmacy can lead to adverse health outcomes in patients, it is a public health concern of greater significance. The contributing factors to polypharmacy may be patient-related or clinician-related. In comparison to other conditions, bipolar disorder is observed to be associated with complex polypharmacy more commonly. Despite the observations, research exploring the prescription patterns in treating patients with bipolar disorder and the practice of polypharmacy is limited. The present perspective illuminates the significance of prioritizing investigative explorations into prescription patterns and polypharmacy, focusing on bipolar disorder, and proposes an uncomplicated conceptual study design that can be utilized to conduct investigative explorations in the local context.

**Keywords:** Psychotropic polypharmacy, prescription patterns, bipolar disorder

### 1. Background

Psychotropic polypharmacy, which is the use of two or more psychotropic drugs in the same patient could be of two types—namely, simple psychotropic polypharmacy (SPP) and complex psychotropic polypharmacy (CPP). SPP refers to the use of only two psychotropic drugs in the same patient, while CPP refers to the use of three or more psychotropic drugs or four or more psychotropic drugs in the same patient (Govaerts et al., 2021; Kim et al., 2021). Commonly prescribed psychotropic drug groups may include antidepressants, antipsychotics, hypnotics, tranquilizers, and antiepileptics. Antipsychotics may be first-generation, second-generation, or third-generation. Tranquilizers include the subgroup benzodiazepine, while antidepressants include selective serotonin reuptake inhibitors (SSRI), selective serotonin-norepinephrine reuptake inhibitors (SSNRI), tricyclic antidepressants, and so forth (Seifert et al., 2022). A common practice of polypharmacy is observed in clinical psychiatry, which is generally believed to be driven by clinical experience rather than scientific evidence (Alharbi et al., 2019; Govaerts et al., 2021). Polypharmacy is a significant public health concern as it equips the capacity to threaten the health of patients (Govaerts et al., 2021; Rothschild, 2021). This may occur through adverse drug interactions such as pharmacokinetic interactions and pharmacodynamics interactions, drug-induced liver injury, and increasing the risk of falls among older patients. Polypharmacy may also lead to increased non-compliance among patients to prescribed medication regimens, overdoing of drugs, prescription of contraindicated medication, increased mortality, and increased healthcare expenditure (Alharbi et al., 2019; Govaerts et al., 2021; Kim et al., 2021; Rothschild, 2021).

Factors contributing to polypharmacy could be patient-related, clinician-related, or other. Clinician-related factors may include adding new drugs to the medication regimen of patients without de-prescribing drugs that are potentially ineffective. Carrying over drugs prescribed previously by other treating clinicians without considering their necessity, efficacy, and tolerance and not optimizing the dosing of appropriate drugs may also act as clinician-related factors (Govaerts et al., 2021; Kim et al., 2021). Patient-related factors may include the patient's personality and the patient's expectations (Govaerts et al., 2021; Kim et al., 2021). Other

factors that may contribute to polypharmacy could be the absence or lack of clear guidelines on the introduction of more approved drugs and the appropriate discontinuation of certain drugs (Kim et al., 2021).

The current clinical practice in psychiatry, however, is often oriented towards polypharmacy when treating chronic psychiatric conditions such as schizophrenia, bipolar disorder, and epilepsy (Adachi et al., 2021). Bipolar disorder, for example, was observed to be associated with CPP more commonly in comparison to other conditions (Kim et al., 2021). Despite the common observation of polypharmacy, research exploring this domain is limited (Adachi et al., 2021; Golden et al., 2017; Kim et al., 2021; Rothschild, 2021). Therefore, the present perspective aims to illuminate the significance of prioritizing investigative explorations into prescription patterns and polypharmacy, focusing primarily on bipolar disorder.

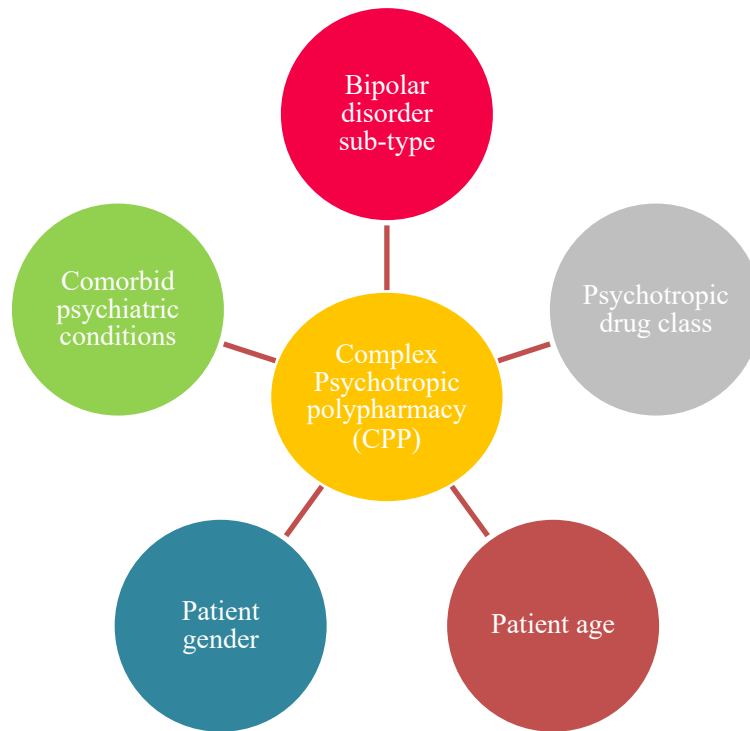
## **2. Bipolar disorder-associated psychotropic polypharmacy**

Bipolar disorder is a chronic cyclical mood disorder, which is common in clinical practice (Fung et al., 2019; Reiser, 2015; Yatham et al., 2018). It causes unusual changes in an individual's mood, energy, activity levels, and concentration. The changes in mood may range from manic (extremely elated, irritable, or energized) episodes, to hypomanic (less severe manic) episodes to depressive (sad, indifferent, or hopeless) episodes. Some individuals may have both manic and depressive symptoms in the same episode (episode with mixed features) (National Institute of Mental Health, 2023). The onset may occur more commonly in late adolescence and early adulthood (National Institute of Mental Health, 2023; Yatham et al., 2018). It impacts many functional domains of individuals and is associated with significant morbidity, mortality, increased healthcare costs, and utilization of healthcare services (Fung et al., 2019; Reiser, 2015; Yatham et al., 2018). Bipolar disorder encompasses three main subtypes, namely, bipolar I disorder, bipolar II disorder, Cyclothymic disorder, or Cyclothymia (National Institute of Mental Health, 2023; Yatham et al., 2018). Comorbid psychiatric disorders such as anxiety disorder, attention-deficit/hyperactivity disorder (ADHD), and substance use disorder are more often observed among individuals with bipolar disorder. Additionally, symptoms of psychosis such as hallucinations and delusions may at times present in individuals with severe manic or depressive episodes (National Institute of Mental Health, 2023). Pharmacological agents incorporated for treatment may include conventional mood stabilizers, antidepressants, antipsychotics, and benzodiazepines (Grover et al., 2021). The treatment of bipolar disorder often involves polypharmacy (Grover et al., 2021). For example, prescribing an SSRI plus mirtazapine with lithium or venlafaxine, or divalproex (Kim et al., 2021). However, simple polypharmacy is a recognized initial treatment strategy, which is also incorporated into clinical practice (Kim et al., 2021). On the contrary, treatment incorporating CPP may lead to adverse health outcomes. These may include increased occurrence of adverse side effects and drug interactions, poor medication adherence, increased comorbid medical conditions, and higher healthcare costs (Fung et al., 2019; Golden et al., 2017). The underpinning factors attributable to the observed bipolar disorder-associated CPP may include complex symptom presentation (an episode with mixed features, psychosis, circadian dysrhythmias) among patients with bipolar disorder, suicide attempts, and comorbid psychiatric disorders (Adachi et al., 2021; Fung et al., 2019; Kim et al., 2021).

Despite the observed adverse health outcomes, the practice of CPP has been observed to increase over the years (Fung et al., 2019; Rothschild, 2021). However, prescription patterns may vary across countries (Alharbi et al., 2019). Surprisingly, research exploring prescription patterns for bipolar disorder and polypharmacy is limited (Amerio et al., 2021). Therefore, understanding the prescription patterns for bipolar disorder locally is of utmost significance, especially in identifying whether polypharmacy is practiced, including its extent to avert potential adverse health outcomes in patients with bipolar disorder. Not surprisingly, information on prescription patterns for bipolar disorder and research investigating the practice of polypharmacy is scarce in Sri Lanka. Until the present day, only one study (Lin et al., 2022) has explored the prescription patterns in patients with bipolar disorder and the prevalence of CPP among those patients. However, the sample size incorporated in their study was small. Therefore, the present perspective proposes an uncomplicated conceptual study design that can be utilized to conduct investigative explorations into the practice of CPP in treating bipolar disorder in the local context.

### 3. A conceptual study design to explore CPP

A cross-sectional study design can be employed as it allows the researcher to determine the prevalence of exposure variables and the outcome variable of interest in a defined population and time (Setia, 2016). It further allows the identification of any associations between the outcome variable of interest and multiple exposure variables of interest (Aggarwal & Ranganathan, 2019; Setia, 2016; Wang & Cheng, 2020). Furthermore, cross-sectional study design is identified to be the most suitable for determining prevalence (Wang & Cheng, 2020). The present study design is conceptualized to determine the prevalence of CPP among patients with a primary diagnosis of bipolar disorder, including the prevalence of CPP according to the subtype of bipolar disorder, psychotropic drug class, age of the patient, gender of the patient, and the presence or absence of comorbid psychiatric conditions.



**Figure 1:** Exposure variables of interest for determining complex psychotropic polypharmacy (CPP) in patients with bipolar disorder

Thus, the outcome variable is the prevalence of CPP, which is the use of three or more psychotropic drugs in the same patient (Kim et al., 2021). Exposure variables are (1) subtype of bipolar disorder, (2) psychotropic drug class, (3) age of the patient, (4) gender of the patient, and (5) presence or absence of comorbid psychiatric conditions. The subtype may be assessed through the DSM-5-TR criteria (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision) by the American Psychiatric Association (American Psychiatric Association, 2022) and the ICD-11 (International Classification of Diseases, 11th edition) criteria (World Health Organization, 2023). The psychotropic drug class may be determined using the Anatomical Therapeutic Chemical (ATC) Classification System with Defined Daily Doses (DDD) Index 2024 (WHO Collaborating Centre for Drug Statistics Methodology, 2023). The drugs may be classified as mood stabilizers, antipsychotics, antidepressants, and benzodiazepines (Caraci et al., 2017; Hu et al., 2022). Since the age of the patient and gender of the patient were believed to be associated with CPP (Kim et al., 2021), they are incorporated into the study design as exposure variables. The age of the patients may be categorized as 18 to 50 years and over 50 years. Exploring the presence or absence of comorbid psychiatric conditions is important as patients with a primary diagnosis of bipolar disorder tend to have one or more other psychiatric disorders such as anxiety disorder and substance use disorder (National Institute of Mental Health, 2023; Yatham et al., 2018). The study design may also incorporate the site if the

study is intended to be carried out in several locations such as outpatient psychiatric clinics in several tertiary care institutions.

#### 4. Significance of investigative exploration

Research that investigates prescription patterns in treating patients with bipolar disorder and the practice of CPP in their treatment is minimal, especially in the local context. However, it is of utmost importance to explore this domain due to the increased occurrence of adverse side effects and drug interactions, poor adherence to medication, and healthcare expenditure in employing CPP in treating patients with bipolar disorder. More importantly, bipolar disorder is associated with comorbid medical conditions, including but not limited to cardiovascular diseases, endocrine diseases, and respiratory diseases (Wang et al., 2022). Furthermore, explorations into prescription patterns and the practice of CPP would help in reducing the drug burden for patients with bipolar disorder, especially for patients with no apparent benefit from using complex drug regimens. This would further help in preventing or minimizing the occurrence of unintended adverse effects. Finally, the patterns observed can be used to inform guidelines for treating clinicians on the prescription of certain psychotropic medications and create policies to prevent unwarranted psychotropic polypharmacy to facilitate appropriate, safe, and effective delivery of care for patients.

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