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# **Rational Polypharmacy in Psychiatry**

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Additional information is available at the end of the chapter

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## **1. Introduction**

Dimensional approach in clinical psychopharmacology conceptualizes a disorder under multiple dimensions that are affected at a particular time. Impairments in multiple domains is a major factor leading to the fact that significant proportion of patients with various major psychiatric disorders does not achieve remission (McEvoy et al., 2006; Perlis et al., 2006; Rush et al., 2006). This model proposes to tackle each dimension independently as the interaction between the various dimensions remains to be accurately understood (Baruch et al., 1992). Such an approach has lead to use of several molecules in the treatment of a single condition, a situation that we often refer to as polypharmacy. Increasing frequency of polypharmacy (Mojtabai and Olfson, 2010) suggests that the major approach in pharmacological treatment of psychiatric disorders is the dimensional one.

Psychiatry being one of the most complex specialties among medicine, psychiatric diagnosis is based on subjective personal history and specifically constructed clinical criteria. There is a certain lack of empirical data and more so for objective laboratory tests. Moreover, with the increasing identification of comorbid conditions and evidence-based guidelines recommending an array of molecules in the treatment of a single disorder, without the emphasis on, preference has escalated the strategy of polypharmacy. The reported overall prevalence rates of polypharmacy in psychiatry vary between 13% to an alluring 90% (Kukreja et al., 2013).

## **2. Definition and classification**

Although the term polypharmacy has been in use and has evolved for a very long time, a proper definition is still lacking. Majority of studies in psychiatry have used the criteria of “2

or more medications of the same chemical class or with the same or similar pharmacological actions to treat the same condition” (Kukreja et al., 2013). Apart from a trendy yet justifiable classification of polypharmacy into-“The Good, the Bad, and the Ugly” (Kingsbury and Lotito, 2007), several other classifications have been proposed to describe various types of polypharmacy (Table 1). Multiclass Polypharmacy is the most common type with prevalence of 20.9% among which combination of SSRI with a benzodiazepine is the most common. In the same class polypharmacy, treatment with several benzodiazepines is the most common (De las Cuevas and Sanz, 2004).

The basis for these classifications is discrete and hence there would be significant overlap when considering them together i.e. combination of lithium and fluoxetine in treating resistant depression is an example of therapeutic, multiclass, minor and rational polypharmacy. As positive outcome is the foundation for evidence based treatment, contra-therapeutic and rational polypharmacy are mutually exclusive. However, with wide inter-individual heterogeneity, one may consider none of the classes to be exclusively inseparable i.e. rational strategy of clozapine augmentation with olanzapine might result in worsening of metabolic status, resulting in contra-therapeutic polypharmacy.

Sl.no	Classification	Basis	Proposed by
1	<ul style="list-style-type: none"><li>• Therapeutic</li><li>• Contra-therapeutic</li></ul>	Outcome	Werder and Preskorn, 2003
2	<ul style="list-style-type: none"><li>• Same class</li><li>• Multiclass</li><li>• Adjunctive</li><li>• Augmentative</li><li>• Total</li></ul>	Pharmacological class and appropriateness	National Association of State Mental Health Program Directors, 2001
3	<ul style="list-style-type: none"><li>• Minor</li><li>• Moderate</li><li>• Major</li></ul>	Number of drugs	Veehof et al., 2000
4	<ul style="list-style-type: none"><li>• Rational</li><li>• Irrational</li></ul>	Rationality/ evidence base	Kingsbury et al., 2001

**Table 1.** Polypharmacy-several classifications

This narrative review considers various rational polypharmacy strategies in treating psychiatric disorders. Evidence base for polypharmacy strategies in individual disorders is highlighted with an emphasis on special settings.

### 3. Depression

Polypharmacy in the treatment of depression has an increasing trend. While 3.3% of depression patients received 3 or more drugs in 1970s, in 1990s the rate increased to 43.8% in an NIMH hospital (Frye et al., 2000). Although the exact share of rational polypharmacy could not be ascertained, evidence base for polypharmacy in depression management is satisfactory.

With a number of molecules with different mechanisms of action available, combination of any two compounds has a potential for an impressive strategy to treat depression that does not respond to antidepressant monotherapy (Moret, 2005). Combinations of certain antidepressants-mirtazapine combined with venlafaxine, fluoxetine and bupropion (in the order of highest response) have been shown to have better response rate than antidepressant monotherapy (fluoxetine plus placebo) (Blier et al., 2010). Blier and colleagues had also found that a combination of mirtazapine and paroxetine showed significantly higher response rates than either drug alone (Blier et al., 2009). There has been another study (Carpenter et al., 2002) that studied a selective serotonin reuptake inhibitor (SSRI) combined with mirtazapine and found the combination to be better. Nelson et al. (2004) found a combination of fluoxetine and desipramine to be better than either drug alone. Recently, Sung et al. (2012) compared escitalopram monotherapy with bupropion+escitalopram and venlafaxine+mirtazapine and found that there was no significant difference in the adverse effect profile in both chronic and non chronic depression patients. However, they found no significant difference in either response or remission rates between the different treatment groups. Positive data from controlled trials on antidepressant combinations are restricted to mirtazapine as the combination drug questioning the generalizability of the findings to other combinations. Also these trials are not free of limitations: insufficient duration, lower doses of monotherapy agents, etc. (Rush, 2010). Trials including other agents like SAM (S-adenosyl-L-methionine) are not randomized controlled (Alpert et al., 2004).

Various augmentation drugs used in the treatment of depression in combination with an antidepressant are atypical antipsychotics, lithium, hormonal drugs like thyroxine, estrogen and mifepristone, 5HT<sub>1A</sub> antagonists like pindolol, buspirone, and, stimulants like methylphenidate. Augmentation with atypical antipsychotics has been shown to be significantly more effective than placebo for response and remission. Although aripiprazole is the first pharmacologic agent of any type to be approved by the U.S. FDA for use as an augmentation agent in major depressive disorder, other agents have also been used. Among atypical antipsychotics, evidence is available for olanzapine in combination with fluoxetine, quetiapine and aripiprazole in combination with either SSRI or an SNRI and risperidone with various antidepressants (Nelson and Papakostas, 2009). While the meta-Analysis by Nelson and Papakostas (2009) conclude no significant differences in efficacy among the different agents, Connolly and Thase (2011) in their review give a preference to quetiapine and aripiprazole. Bauer et al. (2010) in their meta-analysis found significantly greater mean response rate in the lithium group than the placebo group. Apart from stating augmentation of antidepressants with lithium as the best-evidenced augmentation therapy in the treatment of depression, they also suggested a predictive role of the -50T/C single nucleotide polymorphism of the GSK3-beta gene (Bauer

et al., 2010). However, Connolly and Thase (2011) question its generalizability stating lithium is only effective for use in combination with tricyclic antidepressants (TCAs) and that these trials included less treatment-resistant subjects than those who typically receive TCAs in current clinical settings. Triiodothyronine augmentation seems to offer better benefit/risk ratio for augmentation of modern antidepressants (Connolly and Thase, 2011). While trials on pindolol have failed to replicate positive effects, there is no clear consensus of the role of buspirone, mifepristone and methylphenidate (Moret, 2005). Although estrogen augmentation is effective, the response seems to be more restricted to menopausal women (Liu et al., 2004).

Surprisingly however, data from trials on combination of conventional antidepressants like tricyclic agents and MAO inhibitors or augmentation with first generation antipsychotics is sparse.

## **4. Bipolar disorder**

### **4.1. Acute mania**

In reality, less than 10% of acutely manic patients receive monotherapy. Clinical routine appears to be based on polypharmacy in bipolar patients (Peh and Tay 2008). In line with this clinical practice, RCT's suggest that addition of an antipsychotic to patients with persistent manic symptoms despite treatment with lithium or valproate has shown greater rates of acute efficacy than has continuation of lithium or valproate alone (Vieta et al., 2008). As to the important clinical question whether de novo combinations are better, there is very limited data. A greater efficacy of combination treatment is also supported by a meta-analysis of Smith et al. (2007) which showed that significantly more participants on co-therapy met the response criterion reductions. Such effects were demonstrated for haloperidol, olanzapine, risperidone and quetiapine when administered as co-therapy compared with monotherapy with lithium or valproate. Taken together, there is not enough unambiguous evidence that supports combination therapy as a general first line treatment (Grunze et al., 2009).

### **4.2. Acute bipolar depression**

In the case of acute bipolar depression, the categories of evidence and grades of recommendation for pharmacological treatment are mentioned in table 2. Olanzapine+fluoxetine (Tohen et al. 2003; Brown et al. 2009), Lamotrigine+Lithium (van der Loos et al. 2009), Modafinil+ongoing treatment (Frye et al. 2007) and N-acetylcysteine+Lithium or Valproate (Berk et al. 2008) have been investigated in controlled studies and have positive evidence. Other combinations are either not studied under controlled conditions or have shown inconsistent results (Grunze et al., 2010).

### **4.3. Bipolar disorder prophylaxis**

In routine practice, combination treatments are regularly employed to enhance efficacy of maintenance treatment and to address sub-syndromal symptoms or functional impairment.

Combination and Augmentation Treatments	Category of Evidence	Recommendation Grade
Olanzapine + Fluoxetine	Limited positive evidence from controlled studies	3
Lamotrigine + Lithium	Limited positive evidence from controlled studies	3
Modafinil + ongoing treatment	Limited positive evidence from controlled studies	3
N-acetylcysteine + Lithium or Valproate	Limited positive evidence from controlled studies	3
Sertraline + Lithium or Valproate	Evidence from uncontrolled studies	4
Tranlycypromine + ongoing treatment	Evidence from uncontrolled studies	4
Venlafaxine + Lithium or Valproate	Evidence from uncontrolled studies	4
L-Thyroxine + ongoing treatment	Evidence from uncontrolled studies	4
Topiramate + Lithium or Valproate	Evidence from uncontrolled studies	4
Zonisamide + Lithium or Valproate	Evidence from uncontrolled studies	4
Imipramine + Lithium	Inconsistent results	5
Inositol + Lithium or Valproate	Inconsistent results	5
Omega 3 fatty acids + Lithium or Valproate	Inconsistent results	5
Paroxetine + Lithium or Valproate	Inconsistent results	5
Bupropion + Lithium or Valproate	Inconsistent results	5
Gabapentin + ongoing treatment	Inconsistent results	5

**Table 2.** Categories of evidence and grades of recommendation for acute bipolar depression (Adapted from Grunze et al.(2010))

For example, prospective data of the Stanley Foundation Bipolar Network showed that over 55% of bipolar patients were on two or three medications, 31.8% required four or more drugs and 13.8% requiring five or more medications, but still it took a mean time of 1.5 years to achieve a sustained remission (Post et al., 2010). Positive placebo-controlled RCTs exist for combination treatments of mood stabilizers-valproate+lithium (Geddes et al., 2010), valproate or lithium, with all atypical antipsychotics that have a license for bipolar maintenance treatment – aripiprazole (Marcus et al., 2011), quetiapine (Vieta et al., 2008; Suppes et al., 2009), risperidone (Yatham et al., 2003) and ziprasidone (Bowden et al., 2010). The treatment of bipolar disorder patients may also change frequently in response to side effects, emerging comorbidities including physical health issues and other needs to be specifically tailored for each patient. These needs in real world patients are virtually impossible to capture in a guideline whose focus is the efficacy of a given combination treatment over a limited time period and in a fair proportion of patients. These limitations should be kept in mind when interpreting data of randomized controlled combination maintenance studies. For this reason, various guidelines do not make a special note or recommendation for specific combination treatments (Grunze et al., 2013).



## 5. Anxiety disorder

Benzodiazepines are used in combination with serotonergic drugs during the initial phase-a week or two, before the onset of anti-anxiety effect, either to hasten its efficacy or to suppress the activating side effects that are seen when serotonergic therapy has been started. In the treatment of panic disorder, there is persistent positive evidence from randomized controlled studies for the combination of antidepressants and benzodiazepines (clonazepam plus paroxetine or sertraline) (Pollack et al. 2003; Goddard et al. 2001). But evidence for other combinations is only from uncontrolled studies or case reports. Combination of antidepressants and benzodiazepines also has positive results from controlled data in the management of generalized anxiety disorder and social anxiety disorder. Combination of SSRI and atypical antipsychotics in the treatment of generalized anxiety disorder too has positive evidence from controlled trials (Bandelow et al., 2008). Although an array of combination, adjuvant, augmentation strategies are proposed for the treatment of OCD and PTSD, especially treatment resistance, only augmentation of SSRI with antipsychotics has positive evidence from controlled studies (Bandelow et al., 2008). Rest of the evidence is from uncontrolled data. Table 3 shows various combination regimens in the treatment of anxiety disorders with the recommendation grades.

Diagnosis	Combination and Augmentation Treatments	Category of Evidence	Recommendation Grade
<b>PANIC DISORDER</b>	1. Antidepressants + Benzodiazepines	Full evidence from controlled studies	2
	2. SSRIs+TCAs	Evidence from uncontrolled studies	4
	3. SSRI+Olanzapine		
	4. SSRI+Pindolol or TCAs		
	5. Valproate+Clonazepam	Evidence from case reports	4
	6. Lithium+Clomipramine		
<b>GAD</b>	1. Antidepressants+ Benzodiazepines	Full evidence from controlled studies	2
	2. SSRI+atypical antipsychotics (risperidone or olanzapine)	Limited positive evidence from controlled studies	3
<b>SOCIAL PHOBIA</b>	1. Antidepressants+ Benzodiazepines	Limited positive evidence from controlled studies	3
	2. SSRI+Buspirone	Evidence from uncontrolled studies	4
<b>OCD</b>	1. SSRI+antipsychotics(haloperidol, quetiapine, olanzapine and risperidone)	Limited positive evidence from controlled studies	3
	2. Citalopram+Reboxetine	Evidence from uncontrolled studies	4
	3. SSRI+Clomipramine		
	4. Clomipramine+Lithium		

Diagnosis	Combination and Augmentation Treatments	Category of Evidence	Recommendation Grade
PTSD	5. SSRI+Buspirone	Limited positive evidence from controlled studies	3
	6. SSRI+Topiramate		
	7. Clomipramine+L-tryptophan	Evidence from uncontrolled studies	4
	8. SSRI+Pindolol+L-tryptophan		
	1. Adjunctive olanzapine or risperidone	Evidence from case reports	4
	2. SSRI+Triiodothyronine		
	3. Imipramine+Clonidine	Evidence from case reports	4
	4. Venlafaxine+Quetiapine		
	5. SSRI+Gabapentin	Evidence from case reports	4

**Table 3.** Categories of evidence and grades of recommendation for anxiety disorders (Adapted from Bandelow et al. (2008))

## 6. Schizophrenia

Even on antipsychotic therapy patients with schizophrenia achieving full remission are only about 30% (Hert et al., 2007). Although clozapine has significantly greater efficacy compared to other antipsychotics when unresponsive to either typical or an atypical antipsychotic when used first, its use is associated with significant adverse effects (Kane et al., 1988). Combination therapy is one of the strategies to manage such unresponsiveness. Polypharmacy therapy in the treatment of schizophrenia might be either antipsychotics' combination or an antipsychotic combined with an agent not used primarily for treatment of psychosis but has an augmentative effect. It was observed that at baseline, many schizophrenia patients included in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial were on poly-pharmacotherapy-4% taking lithium, 15% other mood stabilizers, 38% antidepressants, 22% anxiolytics and 6% two antipsychotics (Chakos et al., 2006).

Mood stabilizers like lithium, carbamazepine and valproate have been used as adjuvants to antipsychotic treatment in schizophrenia. While randomized trial-based evidence is available for valproate and carbamazepine, no randomized controlled trials have investigated the effect of lithium in patients with schizophrenia. Patients receiving lithium augmentation showed clinically significant response; this significance was however lost when only patients with non affective symptoms were included (Leucht et al., 2007a). Data based on randomised trials suggests that there is no conclusive evidence to recommend either valproate or carbamazepine is useful as an adjunctive therapy in schizophrenia treatment. However in patients with schizophrenia, positive effects on aggression and tardive dyskinesia with valproate and on violence and EEG abnormalities with carbamazepine have been found (Leucht et al., 2007b; Schwarz et al., 2008).

None of the studies investigating the effect of other augmentation strategies like benzodiazepines, beta-blockers, antidepressants, anti-inflammatory agents, glutamatergic agents, and



electroconvulsive therapy have been able to demonstrate significant improvement in patients with schizophrenia (Correll et al., 2009). Correll et al. (2009) identified certain clinical situations where antipsychotic co-treatment i.e. combining two antipsychotics are superior to antipsychotic monotherapy. Both acute exacerbations and chronically continuous course, co-starting second antipsychotic when compared to augmentation and, co-treatment including clozapine when compared to a strategy not including clozapine, have been found significant improvements in clinical symptomatology when managed with antipsychotic co-treatment than with monotherapy. Among the types of combinations: co-treatment with a typical agent and an atypical agent has been found to be better than a combination of either two typical or atypical agents. In a recent review, Ballon and Stroup (2013) question the generalizability of these findings by commenting that these significant effects would disappear with exclusion of studies from China. We agree to their remark on doubtfulness of replicating the in-vitro model that presumes modulating the schizophrenia pathophysiology at a receptor level citing the limitations in conducting proper clinical trials. Moreover, no guidelines suggest comparative evidence of individual molecules.

Moreover, evidence for efficacy of clozapine augmentation is also currently sparse. Efficacy of adjunctive AEDs like lamotrigine and topiramate, SSRIs like citalopram and co-treatment with other antipsychotics like sulpiride is based on single studies, that too with inconsistent findings (Sommer et al., 2012). Despite their popularity, pharmacological augmentations of clozapine are yet to be demonstrated to be superior to placebo. However, a recent metaanalysis, supports clozapine augmentation with amisulpride and aripiprazole, mirtazapine and ethyl eicosapentaenoic acid (Porcelli et al., 2012).

## 7. Substance use disorders

### 7.1. Alcohol use disorders

Antipsychotics, especially haloperidol, have been used in combination with a BZD for treatment of severe agitation in alcohol withdrawal delirium (Mayo-Smith et al. 2004); however there are no placebo-controlled trials available. Carbamazepine in combination with tiapride has also been found to be effective in treatment of this condition (Soyka et al., 2006). Although, minimal amount of evidence is available, antipsychotic treatment in combination with benzodiazepines is warranted in the treatment of alcohol related psychosis (Soyka et al., 2011). For relapse prevention, disulfiram is considered a second-line medication that can be combined with either naltrexone or acamprosate (Soyka et al., 2011). Although positive open trials are present (Feeney et al. 2006), a recent controlled trial, COMBINE failed to show that acamprosate is effective in relapse prevention, either alone, or in combination with naltrexone (Anton et al. 2006). Ait-Daoudet et al. (2001) found combination of ondansetron and naltrexone reduces craving.

## 7.2. Opioid use disorders

A combination of naloxone and flumazenil has been shown to be significantly effective in treating opioid intoxication with additional benzodiazepine use (Megarbane et al., 2010). Commonly used combination of clonidine and naltrexone has been regarded as safe and effective for rapid detoxification (Kleber et al. 2007). More importantly, combination of buprenorphine and naloxone has excellent evidence in the treatment of opioid withdrawal. Evidence also supports the use of clonidine and lofexidine as adjunctive medications (Soyka et al., 2011).

## 8. Epilepsy

Initial treatment of epilepsies is usually a single antiepileptic drug. However in resistant cases, strategies like alternate monotherapy or polytherapy are suggested. As alternative monotherapy is less common because of the limited efficacy and possible side effects of drugs, polytherapy is commonly initiated when monotherapy fails to control seizures (Bauer et al., 1998). Although there is satisfactory evidence on initial monotherapy, data on long term effectiveness or subsequent polypharmacy regimens is lacking; more so with older antiepileptic drugs (AEDs). Trials have shown that adjunctive therapy with newer AEDs (levetiracetam, oxcarbazepine and topiramate) was favorable than when compared to placebo (Wilby et al., 2005). Costa et al (2011) in a systematic review and meta-analysis of trials comparing a new add-on antiepileptic drug treatment with placebo or drug, found a relatively small magnitude to allow a definitive conclusion about which new antiepileptic drug has superior effectiveness. However these trials are of short duration and often fail to limit inclusion to either partial or generalised seizures. Adjunctive treatment with benzodiazepines also has a poor fund of evidence.

## 9. Child and geriatric populations

One third of pharmacologically treated mentally ill children and adolescents receive polypharmacy, with a remarkable increase in the number of children receiving two or more medications in the past decade (McIntyre and Jerell, 2009)

Psychiatric polypharmacy is common in child and adolescent and geriatric population as well. With a prevalence of multi-class polypharmacy in child and adolescent population to be 19%, antidepressants are the most commonly co-prescribed drugs followed by attention deficit and hyperactivity disorder (ADHD) medications, antipsychotics, mood stabilizers and benzodiazepines (Comer et al., 2010). Except for a few open label studies (Kowatch et al., 2003), data from randomized controlled trials is lacking in this group. Interactions between the various molecules in childhood disorders are remarkable. While methylphenidate did not improve symptoms of ADHD compared to placebo in children and adolescents with bipolar disorder stabilized on aripiprazole, this agent could improve ADHD symptoms in those taking lithium

and valproate (Zigman and Blier, 2012). Such noteworthy interactions suggest empirical rational polypharmacy rather than evidence based polypharmacy.

Similar comment on geriatric population also can be made. Psychiatric polypharmacy in this population is very common (Loyola et al., 2008) and the major reason for such an approach is the presence of medical comorbidities, where evidence base is intricate to build.

### **9.1. Dementia**

Polypharmacy in the treatment of dementia has some evidence base. The rational is that combination therapy of drugs with different modes of action might have a synergistic effect (Ihl et al., 2011). There are randomized controlled trials that investigated the efficacy of combination of memantine with various cholinesterase inhibitors and galantamine. However, there is no conclusive evidence as these studies report both positive and negative results (Dantoine et al., 2006, Ihl et al., 2011, Kornhuber et al., 2009, Porsteinsson et al., 2008). There is some evidence from uncontrolled open studies on the effect of donepezil and ginkgo biloba combination, but negative (Yancheva et al., 2007).

## **10. Medical comorbidity**

Polypharmacy in patients with medical comorbidity is a rule, however, evidence based pharmacological treatment in such conditions is very scarce, in fact less applicable. One important reason is that these subjects are not eligible for most clinical trials (Zimmerman et al., 2002). It is difficult to conduct randomized controlled trials on these subjects as there would be obvious complicatedness in setting the inclusion and exclusion criteria. It is recommended that clinicians should opt for individualized or empirical polypharmacy.

## **11. Individualized rational polypharmacy**

Kingsbury et al. (2001) divided rational polypharmacy into two types: validated and empirical. Validation or evidence base is based on results from controlled trials or meta-analyses. These results guide treatment presuming homogeneity in the illnesses, which hardly exists. Empirical rational polypharmacy is more individualized. Hence empirically this classification can be restated into “standardized” and “individualized” rational polypharmacy. Standardized rational polypharmacy refers to the validated strategies that have been discussed so far. Individualized rational polypharmacy is based on a complete evaluation of the index patient-timing and characterization of various manifestations, a proper evaluation of response to drugs in other affected family members and conducting mini investigations in the background of adequate knowledge of pharmacogenomics, receptor profiles and rating of psychopathology. Clinicians with proper training and motivation only could go ahead with this strategy; otherwise these tactics would end up in contra-therapeutic polypharmacy.

## 12. Causes of irrational polypharmacy and ways to tackle them

Apart from practicing rational polypharmacy, clinicians need to understand various reasons and ways to tackle irrational polypharmacy. Several different causes of irrational polypharmacy have been identified (Kingsbury et al., 2001):

1. Fear and laziness. Continuing the earlier prescribed drug/s that has/have not shown improvement along with the later drug after addition of which there is some response; continuing the drug that was added to ameliorate acute symptoms even after the primary drug's later onset of action has begun.
2. Sloppy diagnosis/ overdiagnosis: such as that of schizoaffective for affective symptoms which could be a part of schizophrenia or for psychotic agitation misdiagnosing it as an affective manifestation.
3. Improper titration. Mistaking the effect of the second drug to be due to a combination of both amidst of the cross titration process.
4. Blind adherence to maximum doses. 80% response on 'x' dose of a dose (that is considered maximum according to one particular guideline) is added with another drug (even after knowing '2x' dose of the first drug could have been tolerated).
5. Inadequate awareness/ blind disbelief on the therapeutic efficacy of psychotherapeutic strategies
6. Inadequate knowledge or inattention towards receptor profile of the molecules.
7. Adhering to industry sponsored guidelines
8. Magical beliefs/ using methods based on word of mouth.

Apart from these causes, industry driven pressure leading to unethical practice and improper monitoring of drug compliance are also equally responsible for irrational polypharmacy. Zigman and Blier (2012) consider pharmacological characteristics like redundancy (two or more drugs have similar/overlapping mechanism of action), pharmacodynamic and pharmacokinetic interactions also as causes of irrational polypharmacy. Zigman and Blier (2012) also provide certain strategies to tackle irrational polypharmacy.

Firstly, to consider selectively active or multifunctional medications wherever appropriate. Two medications selectively active at two different receptors can be chosen when their action at these receptors is known to improve the clinical condition, whereas two multifunctional medications having more or less similar profile at the target receptor should be avoided in combination. Secondly, to consider various pharmacodynamic and pharmacokinetic interactions of the molecules in use. An acetylcholinesterase inhibitor should be avoided in combination with a drug with potent anticholinergic side effects, whereas using a drug in combination with a cytochrome p450 enzyme inducer reduces the efficacy of the drug and lead to irrational polypharmacy. Another strategy is to allow for adequate dose and duration before considering adjunctive or augmentative strategies. Such strategies although scientific, when

used without the adequate trial of a previous drug, would be labeled irrational. The last strategy is to regularly reassess the efficacy of the ongoing combination treatment. Moreover, a trial of tapering one of the drugs in the combination should be given when the response is adequate and has sustained for a period of time.

Niculescu and Hulvershorn (2010) suggest a personalized tri-dimensional treatment (i.e., concurrent treatment of anxiety, mood, and cognitive abnormalities) plus modulation of environmental factors (e.g., stress). Such an approach involves rational polypharmacy—the combination of three or more medications, each acting primarily on anxiety, mood, or cognition, respectively. Depending on the major pathology, one of these medications is used at a higher dose and the others at lower doses. For example, in schizophrenia, an antipsychotic may be primary at a higher dose, with an anxiolytic and/or mood stabilizer secondary at lower doses. Similarly for mood abnormalities such as bipolar disorder, a mood stabilizer at a higher dose would be the primary approach and an anxiolytic and antipsychotic secondary at lower doses.

Apart from these measures, thorough evaluation of the patient's clinical symptoms and medication history along with assessment of drug compliance is of utmost importance in managing irrational polypharmacy. Obtaining drug levels where applicable and a thorough evaluation of reasons for treatment resistance including ruling out general medical causes is another important action to avoid irrational polypharmacy and provide maximum patient care.

Although not validated, polypharmacy justification checklist, not only to justify rational polypharmacy but also to curb irrational polypharmacy, has been generated by Dr. Clif Tennison, Helen Ross McNabb Center, East Tennessee. It is a 38 item checklist targeting 9 domains (Appendix).

### 13. Indian context

There is some epidemiological data available on psychiatric polypharmacy from India. Polypharmacy is common in India and its prevalence rates range from 9-73% (Padmini et al., 2007; Sawhney et al., 2004). Ramadas et al. (2010) found that antipsychotic polypharmacy is more related to typical than with atypical agents. However recently, Shrivastava et al. (2012) found almost 30% of first episode schizophrenia patients receiving more than one atypical antipsychotic. These studies were limited to a section of geographical area and it would be difficult to generalize these findings to other parts of India. Indian studies that have compared the efficacy of rational polypharmacy with mono-therapies are however lacking. However, the Indian psychiatric society has formulated certain guidelines for combination therapies in various disorders. Although no direct recommendation is available, various comments are made on these regimens (Table 4).



Year	Disorder	Available evidence for polypharmacy regimens and comments
2005	Schizophrenia	<ul style="list-style-type: none"> <li>• Combination of intramuscular haloperidol and lorazepam faster response than haloperidol alone</li> <li>• Adjunct studies in India – all open</li> <li>• Adjunctive medications recommended- Lithium carbonate; Antidepressants; Benzodiazepines; and Anticonvulsants.</li> <li>• No specific guidelines</li> </ul>
2005	Depression	<ul style="list-style-type: none"> <li>• Major depressive disorder with psychotic features require combined use of antidepressant and antipsychotic medication especially fluoxetine and olanzapine combination</li> <li>• An SSRI combined with a TCA induce rapid antidepressant response</li> <li>• First strategy for resistant depression- augmentation with Lithium/Thyroid/Buspirone; next: combination (TCA-SSRI. Bupropion-SSRI) Depression with anxiety: Efficacy of high potency benzodiazepine like alprazolam and clonazepam in combination with antidepressants is beneficial</li> </ul>
2005	Bipolar disorder	<ul style="list-style-type: none"> <li>• Valproate plus haloperidol superior antipsychotic alone in reduction of manic symptoms</li> <li>• Difficulty in assessing benzodiazepine combination due to short treatment durations, distinguishing specific antimanic effects from nonspecific sedative effects.</li> <li>• Lithium plus an antipsychotic and valproate plus an antipsychotic suggest greater efficacy or a more rapid onset of action than with these agents alone</li> <li>• Combination of divalproex plus an SSRI an effective strategy for management of breakthrough depression during maintenance of bipolar I disorder</li> </ul>
2006	Alcohol use disorders	<ul style="list-style-type: none"> <li>• Several animal studies demonstrate combinations of medications e.g. disulfiram +naltraxone, acamprosate +naltraxone are more effective in reducing alcohol intake than these drugs used alone</li> <li>• Myth: Combining more than one treatment method has no advantage.</li> </ul>
2006	Nicotine use disorders	<ul style="list-style-type: none"> <li>• Combining nicotine patch with either nicotine gum or nicotine nasal spray increases long-term abstinence rates over those produced by a single form of nicotine replacement therapy</li> </ul>
2006	Opioid use disorders	<ul style="list-style-type: none"> <li>• In the management of withdrawal, non opioid medications like clonidine, benzodiazepines, NSAIDs or a combination of these.</li> <li>• Rapid detoxification: Naloxone in combination with other medications such as clonidine and benzodiazepines</li> <li>• Naltrexone with clonidine for rapid detoxification is safe and effective</li> <li>• Buprenorphine and naloxone combination utilized for agonist maintenance therapy</li> </ul>
2007	Elderly anxiety disorders	<ul style="list-style-type: none"> <li>• Benzodiazepines may be used to reduce the severity of anxiety, the need for rapid anxiolysis along with SSRIs</li> <li>• Beta blockers may be used as augmenting agents, especially when somatic symptoms of anxiety are prominent</li> <li>• Low dose of a tricyclic antidepressant could be used to treat insomnia associated with anxiety in patients who are receiving SSRI.</li> </ul>
2007	Alzheimer's disease	<ul style="list-style-type: none"> <li>• The use and combinations of pharmacological agents should be decided on a case-by-case basis.</li> </ul>



Year	Disorder	Available evidence for polypharmacy regimens and comments
2007	Elderly depression	• Patients with major depression with psychotic features require combined use of antidepressant and antipsychotic medications
2007	Psychosis in elderly	• Refractory cases may be tried on a combination of clozapine + Amisulpride. • Lithium augmentation, citalopram+methylphenidate, modafinil+floxetine or mirtazapine, dexamethasone plus any antidepressant may be indicated
2008	Depression in children and Adolescents	• Recommendation for adults with TRD may be applicable to youth
2008	ADHD	• Combined pharmacotherapy only to be used when at least two individual agents (initially methylphenidate and dexamphetamine) have failed.

**Table 4.** Data on polypharmacy regimens in the Indian Psychiatric society treatment guidelines

**14. Summary, conclusions and recommendations**

- Following the dimensional approach in treating psychiatric disorders, polypharmacy, specifically, multiclass polypharmacy is very common.
- However, rationality in the approach determines whether the outcome is therapeutic or contra therapeutic.
- A positive evidence base from controlled trials for polypharmacy is highest for-
- Depression (add on)-mirtazapine in combination with SSRI
- Depression (augment)-SSRI s with atypical antipsychotics/lithium
- Acute mania-there is not enough unambiguous evidence that supports combination therapy of antipsychotic+mood stabilizer as a general first line treatment.
- Acute bipolar depression-olanzapine+fluoxetine and lamotrigine+lithium
- Bipolar prophylaxis-valproate+lithium, valproate or lithium, with atypical antipsychotics (aripiprazole, quetiapine, risperidone and ziprasidone).
- Panic disorder-combination of clonazepam plus paroxetine or sertraline.
- Generalized anxiety disorder-combination of antidepressants and benzodiazepines and combination of SSRI and atypical antipsychotics
- Social anxiety disorder-combination of antidepressants and benzodiazepines
- OCD & PTSD-augmentation of SSRI with antipsychotics
- Schizophrenia-valproate and carbamazepine adjuvant treatment; clozapine augmentation with amisulpride and aripiprazole, mirtazapine and ethyl eicosapentaenoic acid
- Alcohol withdrawal delirium-haloperidol used in combination with a BZD

- Opioid withdrawal-naloxone and flumazenil, buprenorphine and naloxone; rapid detoxification-clonidine and naltrexone;
- Focal epilepsies-adjunctive therapy with newer AEDs (levetiracetam, oxcarbazepine and topiramate)
- It is recommended that clinicians should opt for individualized or empirical polypharmacy as it is difficult to conduct randomized controlled trials on these subjects because of obvious complicatedness in setting the inclusion and exclusion criteria and derive/ generalize data from them.
- Use of polypharmacy justification checklist to justify rational polypharmacy and also to curb irrational polypharmacy may be an useful option

## Abbreviations

- 5HT1A-5-hydroxytryptamine 1A
- ADHD-Attention Deficit and Hyperactivity Disorder
- AED-Anti Epileptic Drug
- BZD-Benzodiazepine
- CATIE-Clinical Antipsychotic Trials of Intervention Effectiveness
- EEG-Electroencephalography
- GSK-Glycogen synthase kinase
- MAO-Monoamine oxidase
- NIMH-National Institute of Mental Health
- NSAID-Non-steroidal anti-inflammatory drug
- OCD-Obsessive Compulsive Disorder
- PTSD-Post Traumatic Stress Disorder
- RCT-Randomized Control Trial
- SAM-S-adenosyl-l-methionine
- SNRI-Serotonin-norepinephrine reuptake inhibitor
- SSRI-selective serotonin reuptake inhibitor
- TCA-Tricyclic Antidepressant
- TRD-Treatment Resistant Depression
- U.S. FDA-The United States Food and Drug Administration

## Appendix

### POLYPHARMACY JUSTIFICATION CHECKLIST

	YES	NO
1. Before prescribing polypharmacy:		
a. Thorough evaluation of clinical presentation?	<input type="checkbox"/>	<input type="checkbox"/>
b. Thorough evaluation of diagnosis?	<input type="checkbox"/>	<input type="checkbox"/>
2. Evaluation of medication history:		
a. Efficacy of past medications documented/reviewed?	<input type="checkbox"/>	<input type="checkbox"/>
b. Reported side effects of past medications documented/reviewed?	<input type="checkbox"/>	<input type="checkbox"/>
c. Dose and duration of past monotherapy attempts documented/reviewed?	<input type="checkbox"/>	<input type="checkbox"/>
i. At least 21 days of continuous use at same dose? (Mood stabilizers and antipsychotics may require longer trials.)	<input type="checkbox"/>	<input type="checkbox"/>
ii. 2-to-3 monotherapy trials with drugs from different classes?	<input type="checkbox"/>	<input type="checkbox"/>
iii. Review of diagnosis after failure of several monotherapy trials?	<input type="checkbox"/>	<input type="checkbox"/>
3. Patient compliance:		
a. Review of patient compliance during medication trial(s) documented?	<input type="checkbox"/>	<input type="checkbox"/>
b. Patient involvement in reviewing treatment response and treatment options?	<input type="checkbox"/>	<input type="checkbox"/>
c. Review of simplicity of regimen and avoiding complicated regimen?	<input type="checkbox"/>	<input type="checkbox"/>
4. Evaluation of the current medication regimen:		
a. Rationale for each current medication reviewed?	<input type="checkbox"/>	<input type="checkbox"/>
b. Efficacy of each current medication reviewed?	<input type="checkbox"/>	<input type="checkbox"/>
c. OTC medications, herbal remedies, and illicit drugs reviewed?	<input type="checkbox"/>	<input type="checkbox"/>
d. One-time orders and prn medications reviewed? (If >3/week for 3-4 weeks, these should be considered part of a patient's scheduled medication regimen).	<input type="checkbox"/>	<input type="checkbox"/>
5. Review of medication changes:		
a. Total number of medications reduced before adding new one?	<input type="checkbox"/>	<input type="checkbox"/>
b. Only one medication changed at a time?	<input type="checkbox"/>	<input type="checkbox"/>
c. Medication changes completed? Old medication discontinued after new one at therapeutic level for sufficient period of time?	<input type="checkbox"/>	<input type="checkbox"/>
d. Cross-titrations used only with those medications for which this strategy is required?	<input type="checkbox"/>	<input type="checkbox"/>
6. Demonstrable need:		
a. Medications without clear benefit for target symptoms eliminated?	<input type="checkbox"/>	<input type="checkbox"/>
7. Combined and Augmented Pharmacotherapy:		
a. Justification for same-class polypharmacy clearly documented?	<input type="checkbox"/>	<input type="checkbox"/>
i. Specific targeting of different symptom clusters?	<input type="checkbox"/>	<input type="checkbox"/>
ii. Synergism in the drugs' mechanisms of action?	<input type="checkbox"/>	<input type="checkbox"/>
iii. Augmentation of partial treatment response or nonresponse to monotherapy?	<input type="checkbox"/>	<input type="checkbox"/>
iv. Improved risk/benefit ratio by reducing dosage and adverse effects for improved tolerability of one or both drugs?	<input type="checkbox"/>	<input type="checkbox"/>
b. Failed trials of monotherapy documented?	<input type="checkbox"/>	<input type="checkbox"/>
c. Efficacy data on strategically combined treatments reviewed?	<input type="checkbox"/>	<input type="checkbox"/>
8. Monitoring the risks of polypharmacy:		
a. Drug interactions reviewed?	<input type="checkbox"/>	<input type="checkbox"/>
b. Blood levels monitored periodically, especially with signs of toxicity or with medications likely to have drug interactions?	<input type="checkbox"/>	<input type="checkbox"/>
c. Monitoring of higher-risk combinations:		
i. More than one medication from the same class?	<input type="checkbox"/>	<input type="checkbox"/>
ii. More than two antipsychotic medications?	<input type="checkbox"/>	<input type="checkbox"/>
iii. Combinations with cumulative anticholinergic effects?	<input type="checkbox"/>	<input type="checkbox"/>
iv. Combinations with specific additive organ or system effects? (e.g., Cardiac, Renal, Hepatic, Respiratory, Gastrointestinal, Musculoskeletal)	<input type="checkbox"/>	<input type="checkbox"/>
9. Institutional mechanisms in place:		
a. Peer review	<input type="checkbox"/>	<input type="checkbox"/>
b. Automatic/forced drug interaction reviews	<input type="checkbox"/>	<input type="checkbox"/>
c. Supported access to medication information	<input type="checkbox"/>	<input type="checkbox"/>
d. Pharmacy consultation	<input type="checkbox"/>	<input type="checkbox"/>
e. Drug utilization review	<input type="checkbox"/>	<input type="checkbox"/>

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## References

- [1] Ait-Daoud N, Johnson BA, Prohoda TJ, Hargita ID. 2001. Combining ondansetron and naltrexone reduces craving among biologically predisposed alcoholics: preliminary clinical evidence. *Psychopharmacology* 154:2327.
- [2] Alpert JE, Papakostas G, Mischoulon D, et al. S-Adenosyl-Lmethionine (SAME) as an adjunct for resistant major depressive disorder: an open trial following partial or nonresponse to selective serotonin reuptake inhibitors or venlafaxine. *J Clin Psychopharmacol* 2004;24:661–4.
- [3] Andrade C, Kharawala S. Practice guideline for the pharmacological treatment of anxiety disorders in the elderly. *Indian psychiatric society treatment guidelines* 2007.
- [4] Anton RF, O'Malley SS, Ciraulo DA, et al. 2006. Combined pharmacotherapies and behavioural interventions for alcohol dependence: the Combine study: a randomized controlled trial. *J Am Med Assoc* 295:20032017.
- [5] Avasthi A, Grover S, Bharadwaj R. Clinical Practice Guidelines for Treatment of Depression in Elderly. *Indian psychiatric society treatment guidelines* 2007.
- [6] Avasthi A, Kumar S, Vikas A. Clinical practice guidelines for the management of bipolar affective (mood) disorders. *Indian psychiatric society treatment guidelines* 2005.
- [7] Awasti A. Treatment of Depression in Children and Adolescents. *Indian psychiatric society treatment guidelines* 2008.
- [8] Ballon J, Stroup TS. Polypharmacy for schizophrenia. *Curr Opin Psychiatry* 2013;26(2):208-13.
- [9] Bandelow B, Zohar J, Hollander E, Kasper S, Möller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders-first revision. *World J Biol Psychiatry*. 2008;9(4):248-312.

- [10] Baruch P, Filteau MJ, Bouchard RH, Pourcher E, Vincent P, Jouvent R. The dimensional approach to clinical psychopharmacology: a polysemous concept. *J Psychiatry Neurosci*. 1992;17(2):55-60.
- [11] Basan A, Kissling W, Leucht S. Valproate as an adjunct to antipsychotics for schizophrenia: a systematic review of randomized trials. *Schizophr Res*. 2004;70(1):33-37.
- [12] Bauer J. Anticonvulsant combination therapy: rational concepts versus real effectiveness. *Fortschr Neurol Psychiatr* 1998;66:414-426.
- [13] Bauer M, Adli M, Bschor T (2010) Lithium's emerging role in the treatment of refractory major depressive episodes: augmentation of antidepressants. *Neuropsychobiology* 62: 36-42.
- [14] Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. 2008. N-Acetyl cysteine for depressive symptoms in bipolar disorder— a double-blind randomized placebo-controlled trial. *Biol Psychiatry* 64:468-475.
- [15] Blier P, Gobbi G, Turcotte JE, de Montigny C, Boucher N, Hébert C, Debonnel G. Mirtazapine and paroxetine in major depression: a comparison of monotherapy versus their combination from treatment initiation. *Eur Neuropsychopharmacol* 2009; 19:457-465.
- [16] Blier P, Ward HE, Tremblay P, Laberge L, Hébert C, Bergeron R. Combination of antidepressant medications from treatment initiation for major depressive disorder: a double-blind randomized study. *Am J Psychiatry* 2010; 167:281-288.
- [17] Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry* 2010;71:130-7.
- [18] Brown E, Dunner DL, McElroy SL, Keck PE, Adams DH, Degenhardt E, et al. 2009. Olanzapine/fluoxetine combination vs. lamotrigine in the 6-month treatment of bipolar I depression. *Int J Neuropsychopharmacol* 12(6):773-782.
- [19] Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. *Biol Psychiatry* 2002; 51:183-188.
- [20] Chakos MH, Glick ID, Miller AL, Hamner MB, Miller DD, Patel JK, et al. Baseline use of concomitant psychotropic medications to treat schizophrenia in the CATIE trial. *Psychiatr Serv*. 2006;57:1094-101.
- [21] Comer JS, Olfson M, Mojtabai R. National trends in child and adolescent psychotropic polypharmacy in office-based practice, 1996-2007. *J Am Acad Child Adolesc Psychiatry* 2010;49:1001-10.
- [22] Connolly KR, Thase ME. If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. *Drugs* 2011;71(1):43-64.

- [23] Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophr Bull* 2009;35(2):443-57.
- [24] Costa J, Fareleira F, Ascensão R, Borges M, Sampaio C, Vaz-Carneiro A. Clinical comparability of the new antiepileptic drugs in refractory partial epilepsy: a systematic review and meta-analysis. *Epilepsia* 2011;52:1280-91.
- [25] Dantoin T, Auriacombe S, Sarazin M, Becker H, Pere JJ, Bourdeix I. 2006. Rivastigmine monotherapy and combination therapy with memantine in patients with moderately severe Alzheimer's disease who failed to benefit from previous cholinesterase inhibitor treatment. *Int J Clin Pract* 60:110 – 118.
- [26] De las Cuevas C, Sanz EJ. Polypharmacy in psychiatric practice in the Canary Islands. *BMC Psychiatry* 2004;4:18.
- [27] Desai NG, Kumar R, Sengupta SN, Sharma P. Clinical practice guidelines for treatment of alcohol dependence. *Indian psychiatric society treatment guidelines* 2006.
- [28] Feeney GFX, Connor JP, Young McD, Tucker J, McPherson A. 2006. Combined acamprosate and naltrexone, with cognitive behavioral therapy is superior to either medication alone for alcohol abstinence: A single centre's experience with pharmacotherapy. *Alcohol Alcoholism* 41:321-327.
- [29] Findling RL, Short EJ, McNamara NK, et al. (2007) Methylphenidate in the treatment of children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 46: 1445–1453.
- [30] Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE, Walden J, et al. 2007. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry* 164:1242–1249.
- [31] Frye MA, Ketter TA, Leverich GS, Huggins T, Lantz C, Denicoff KD, Post R. The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. *J Clin Psychiatry* 2000;61:9–15.
- [32] Gautam S, Batra L, Gaur N, Meena PS. Clinical Practice Guidelines for the Assessment and Treatment of Attention-Deficit/Hyperactivity Disorder. *Indian psychiatric society treatment guidelines*. Indian psychiatric society treatment guidelines 2008.
- [33] Gautam S, Batra L, Gawri A. Clinical practice guidelines for management of nicotine dependence. *Indian psychiatric society treatment guidelines* 2006.
- [34] Gautam S, Batra L. Clinical practice guidelines for the management of depression. *Indian psychiatric society treatment guidelines* 2005.
- [35] Gautam S, Bhatia G, Khan A, Odha PI, Gaur N. Clinical practice guidelines on psychoses in elderly. *Indian psychiatric society treatment guidelines* 2007.



- [36] Gautam S, Gupta ID, Nijhawan A, Gaur V. Clinical practice guidelines for management of opioid dependence. Indian psychiatric society treatment guidelines 2006.
- [37] Geddes JR, Goodwin GM, Rendell J, et al. (2010) Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet* 375: 385–395.
- [38] Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, Mattson R, French JA, Perucca E, Tomson T. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2013;54:551-563.
- [39] Goddard AW, Brouette T, Almai A, Jetty P, Woods SW, Charney D. 2001. Early coadministration of clonazepam with sertraline for panic disorder. *Arch Gen Psychiatry* 58:681-686.
- [40] Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, Kasper S. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *World J Biol Psychiatry* 2009;10(2):85-116.
- [41] Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, Kasper S. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry* 2010;11(2):81-109.
- [42] Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, Kasper S. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *World J Biol Psychiatry* 2013;14(3):154-219.
- [43] Hert MD, van Winkel R, Wampers M, et al. Remission criteria for schizophrenia: evaluation in a large naturalistic cohort. *Schizophr Res* 2007; 92:68–73.
- [44] Ihl R, Frölich L, Winblad B, Schneider L, Burns A, Möller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of Alzheimer's disease and other dementias. *World J Biol Psychiatry*. 2011 Feb;12(1): 2-32.
- [45] Kane JM, Honigfeld G, Singer J, Meltzer H. Clozapine in treatment-resistant schizophrenics. *Psychopharmacol Bull*. 1988; 24(1):62–67.
- [46] Kingsbury SJ, Lotito ML. Psychiatric polypharmacy: the good, the bad, and the ugly. *Psychiatric Times* 2007;24(4):NP.
- [47] Kingsbury SJ, Yi D, Simpson GM. Psychopharmacology: rational and irrational polypharmacy. *Psychiatr Serv*. 2001;52(8):1033-6.

- [48] Kleber HD, Weiss RD, Anton RF Jr, George TP, Greenfield SF, Kosten TR, et al. 2007. Treatment of patients with substance use disorders, second edition. *Am J Psychiatry* 164:5 – 123.
- [49] Kornhuber J, Schmidtke K, Frolich L, Perneczky R, Wolf S, Hampel H, et al. 2009. Early and differential diagnosis of dementia and mild cognitive impairment: design and cohort baseline characteristics of the German Dementia Competence Network. *Dement Geriatr Cogn Disord* 27:404 – 417 (Epub 1 April 2009).
- [50] Kowatch RA, Sethuraman G, Hume JH, Kromelis M, Weinberg WA. Combination Pharmacotherapy in Children and Adolescents with Bipolar Disorder. *Biol Psychiatry* 2003;53:978–984.
- [51] Kukreja S, Kalra G, Shah N, Shrivastava A. Polypharmacy in psychiatry: a review. *Mens Sana Monogr*. 2013;11(1):82-99.
- [52] Kulhara P, Chakrabarti S. Clinical practice guidelines for the management of schizophrenia. Indian psychiatric society treatment guidelines 2005.
- [53] Leucht S, Kissling W, McGrath J, White P. Carbamazepine for schizophrenia. *Cochrane Database Syst Rev* 2007b; Issue 3: CD001258.
- [54] Leucht S, Kissling W, McGrath J. Lithium for schizophrenia. *Cochrane Database Syst Rev* 2007a; Issue 3: CD003834.
- [55] Leucht S, McGrath J, Kissling W. Lithium for Schizophrenia (Cochrane Review). *The Cochrane Library*. 2003;Issue 3.
- [56] Leucht S, McGrath J, White P, Kissling W. Carbamazepine for Schizophrenia and Schizoaffective Psychoses (Cochrane Review). *The Cochrane Library*. Issue 2.
- [57] Liu P, He FF, Bai WP, et al. 2004. Menopausal depression: comparison of hormone replacement therapy and hormone replacement therapy plus fluoxetine. *Chin Med J*, 117:189–94.
- [58] Loyola Filho AI, Uchoa E, Firmo JO, Lima-Costa MF. Influence of income on the association between cognitive impairment and polypharmacy: Bambuí Project. *Rev Saude Publica* 2008;42:89–99.
- [59] Marcus R, Khan A, Rollin L, Morris B, Timko K, Carson W, Sanchez R. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. *Bipolar Disord* 2011;13:133–44.
- [60] Mayo-Smith MF, Breecher LH, Fischer TL, et al. 2004. Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Arch Intern Med* 164:1405-1412.

- [61] McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006;163:600–610.
- [62] McIntyre RS, Jerrell JM. Polypharmacy in children and adolescents treated for major depressive disorder: a claims database study. *J Clin Psychiatry* 2009;70:240–246.
- [63] Megarbane B, Buisien A, Jacobs F, Resiere D, Chevillard L, Vicaut E, Baud FJ. 2010. Prospective comparative assessment of buprenorphine overdose with heroin and methadone: clinical characteristics and response to antidotal treatment. *J Subst Abuse Treat* 38:403 – 407.
- [64] Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. *Arch Gen Psychiatry*. 2010;67(1):26-36.
- [65] Moret C. Combination/augmentation strategies for improving the treatment of depression. *Neuropsychiatric disease and treatment* 2005;1(4) 301–9.
- [66] National Association of State Mental Health Program Directors (NASMHPD): Technical Report on Psychiatric Polypharmacy. Medical Directors Council and State Medicaid Directors: Alexandria, Virginia: 2001.
- [67] Nelson JC and Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry* 2009;166:980–91.
- [68] Nelson JC, Mazure CM, Jatlow PI, et al. Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. *Biol Psychiatry* 2004;55: 296–300.
- [69] Niculescu AB, Hulvershorn LA. Toward Early, Personalized, Rational Polypharmacy In Psychiatry: A Tri-Dimensional Approach. *Psychopharm Rev* 2010; 45: 9-16.
- [70] Padmini DD, Amarjeeth R, Sushma M, Guido S. Prescription patterns of psychotropic drugs in hospitalized schizophrenic patients in a tertiary care hospital. *Calicut Med J*. 2007;5:e3.
- [71] Peh AL, Tay LK. Demographical profile and clinical features of patients with bipolar disorder in an outpatient setting in Singapore. *Singapore Medical J* 2008 May;49(5): 380-3.
- [72] Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2006;163:217–224.
- [73] Pollack MH, Simon NM, Worthington JJ, Doyle AL, Peters P, Toshkov F, et al. 2003b. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. *J Psychopharmacol* 17:276-282.

- [74] Porcelli S, Balzarro B, Serretti A. Clozapine resistance: augmentation strategies. *Eur Neuropsychopharmacol* 2012;22:165-182.
- [75] Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT, Memantine MEM-MD-12 Study Group. 2008. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. *Curr Alzheimer Res* 5:83 – 89.
- [76] Post RM, Altshuler LL, Frye MA, Suppes T, Keck PE Jr, McElroy SL, Leverich GS, Luckenbaugh DA, Rowe M, Pizzarello S, Kupka RW, Grunze H, Nolen WA. Complexity of pharmacologic treatment required for sustained improvement in outpatients with bipolar disorder. *J Clin Psychiatry* 2010;71(9):1176-86.
- [77] Ramadas S, Kuttichira P, Sumesh TP, Ummer SA. A study of an antipsychotic prescription pattern of patients with schizophrenia in a developing country. *Indian J Psychol Med* 2010;32:13–6.
- [78] Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer term outcomes in depressed outpatients requiring one or several treatment steps: a STAR\*D report. *Am J Psychiatry* 2006;163:1905–1917.
- [79] Rush AJ. Combining Antidepressant Medications: A Good Idea? *Am J Psychiatry* 2010;167:241-3.
- [80] Sawhney V, Chopra V, Kapoor B, Thappa JR, Tandon VR. Prescription trends in schizophrenia and manic depressive psychosis. *J K Sci.* 2005;7:156–8.
- [81] Scheffer RE, Kowatch RA, Carmody T, et al. (2005) Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *Am J Psychiatry* 162: 58–64.
- [82] Schwarz C, Volz A, Li C, Leucht S. Valproate for schizophrenia. *Cochrane Database Syst Rev* 2008; Issue 3: CD004028.
- [83] Shaji KS. Clinical Practice Guidelines for Management of Alzheimer's Disease. Indian psychiatric society treatment guidelines 2007.
- [84] Shrivastava A, Johnston M, Terpstra K, Stitt L, Shah N. Atypical antipsychotics usage in long-term follow-up of first episode schizophrenia. *Indian J Psychiatry* 2012;54:248–52.
- [85] Smith LA, Cornelius V, Warnock A, Tacchi MJ, Taylor D. Acute bipolar mania: a systematic review and meta-analysis of co-therapy vs. monotherapy. *Acta Psychiatr-Scand* 2007;115:12-20.
- [86] Sommer IE, Begemann MJ, Temmerman A, Leucht S. Pharmacological augmentation strategies for schizophrenia patients with insufficient response to clozapine: a quantitative literature review. *Schizophr Bull* 2012;38:1003-1011.

- [87] Soyka M, Kranzler HR, van den Brink W, Krystal J, Möller HJ, Kasper S. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of substance use and related disorders. Part 2: Opioid dependence. *World J Biol Psychiatry*. 2011 Apr;12(3):160-87.
- [88] Soyka M, Schmidt F, Schmidt P. 2006. Efficacy and safety of outpatient alcohol detoxification with a combination of tiapride/ carbamazepine: Additional evidence. *Pharmacopsychiatry* 39:3034.
- [89] Sung SC, Haley CL, Wisniewski SR, Fava M, Nierenberg AA, Warden D, Morris DW, Kurian BT, Trivedi MH, Rush AJ. The impact of chronic depression on acute and long-term outcomes in a randomized trial comparing selective serotonin reuptake inhibitor monotherapy versus each of 2 different antidepressant medication combinations. *J Clin Psychiatry* 2012;73(7):967-76.
- [90] Suppes T, Vieta E, Liu S, Brecher M, Paulsson B. Maintenance treatment for patients with bipolar I disorder: results from a north american study of quetiapine in combination with lithium or divalproex (trial 127). *Am J Psychiatry* 2009;166(4):476-88.
- [91] Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. 2003. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 60:1079–1088.
- [92] van der Loos ML, Mulder PG, Hartong EG, Blom MB, Vergouwen AC, de Keyser HJ, et al. 2009. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry* 70:223–231.
- [93] Veehof L, Stewart R, Haaijer-Ruskamp F, Jong BM. The development of polypharmacy. A longitudinal study. *Fam Pract*. 2000;17(3):261-7.
- [94] Vieta E, Suppes T, Eggens I, Persson I, Paulsson B, Brecher M. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *J Affect Disord* 2008;109(3):251-63.
- [95] Vieta E, Tjoen C, McQuade RD, Carson WH Jr, Marcus RN, Sanchez R, Owen R, Nameche L. Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. *Am J Psychiatry* 2008;165(10):1316-25.
- [96] Werder SF, Preskorn SH: Managing polypharmacy: Walking the fine line between help and harm. *Current Psychiatry Online* 2003;2(2):published online.
- [97] Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, Mason A, Golder S, O'Meara S, Sculpher M, Drummond M, Forbes C. Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. *Health Technol Assess* 2005;9:1-157.
- [98] Yancheva S, Ihl R, Nikolova G, Panayotov C, Schlaefke S, Hoerr R, for the GINDON Study Group. 2009. Ginkgo biloba extract EGb 761®, donepezil or both combined in



the treatment of Alzheimer's disease with neuropsychiatric features: A randomised, double-blind, exploratory trial. *Aging Ment Health* 13:183 – 190.

- [99] Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A. Mood stabilizers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomized controlled trial. *Br J Psychiatry* 2003;182:141–7.
- [100] Zeni CP, Tramontina S, Ketzer CR, et al. (2009) Methylphenidate combined with aripiprazole in children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder: a randomized crossover trial. *J Am Acad Child Adolesc Psychiatry* 19: 553–561.
- [101] Zigman D, Blier P. A framework to avoid irrational polypharmacy in psychiatry. *J Psychopharmacol.* 2012 Dec;26(12):1507-11.
- [102] Zimmerman M, Mattia JI and Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry* 2002;159:469–473.



