Chapter 5

Rational Polypharmacy in Psychiatry

S. Haque Nizamie and Sai Krishna Tikka

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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	• Therapeutic • Contra-therapeutic	Outcome	Werder and Preskorn, 2003
2	• Same class • Multiclass • Adjunctive • Augmentative • Total	Pharmacological class and appropriateness	National Association of State Mental Health Program Directors, 2001
3	• Minor • Moderate • Major	Number of drugs	Veehof et al., 2000
4	• Rational • Irrational	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.

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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 anti depressant 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+escilatoplram and velnafaxine+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, 5HT1A 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
Tranylcypromine + 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
PANIC DISORDER	1. Antidepressants + Benzodiazepines	Full evidence from controlled studies	2
	2. SSRIs+TCAs 3. SSRI+Olanzapine 4. SSRI+Pindolol or TCAs 5. Valproate+Clonazepam	Evidence from uncontrolled studies	4
	6. Lithium+Clomipramine	Evidence from case reports	4
GAD	1. Antidepressants+ Benzodiazepines	Full evidence from controlled studies	2
	2. SSRI+atypical antipsychotics (risperidone or olanzapine)	Limited positive evidence from controlled studies	3
SOCIAL PHOBIA	1. Antidepressants+ Benzodiazepines	Limited positive evidence from controlled studies	3
	2. SSRI+Buspirone	Evidence from uncontrolled studies	4
OCD	1. SSRI+antipsychotics(haloperidol, quetiapine, olanzapine and risperidone)	Limited positive evidence from controlled studies	3
	2. Citalopram+Reboxetine 3. SSRI+Clomipramine 4. Clomipramine+Lithium	Evidence from uncontrolled studies	4

Diagnosis	Combination and Augmentation Treatments	Category of Evidence	Recommendation Grade
	5. SSRI+Buspirone 6. SSRI+Topiramate 7. Clomipramine+L-tryptophan 8. SSRI+Pindolol+L-tryptophan		
PTSD	1. Adjunctive olanzapine or risperidone	Limited positive evidence from controlled studies	3
	2. SSRI+Triiodothyronine 3. Imipramine+Clonidine	Evidence from uncontrolled studies	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 al. (2001) found combination of ondansetron and naltrexone reduces craving.

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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 gingko 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.

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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).

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Year	Disorder	Available evidence for polypharmacy regimens and comments
2005	Schizophrenia	• Combination of intramuscular haloperidol and lorazepam faster response than haloperidol alone • Adjunct studies in India – all open • Adjunctive medications recommended- Lithium carbonate; Antidepressants; Benzodiazepines; and Anticonvulsants. • No specific guidelines
2005	Depression	• Major depressive disorder with psychotic features require combined use of antidepressant and antipsychotic medication especially fluoxetine and olanzapine combination • An SSRI combined with a TCA induce rapid antidepressant response • 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
2005	Bipolar disorder	• Valproate plus haloperidol superior antipsychotic alone in reduction of manic symptoms • Difficulty in assessing benzodiazepine combination due to short treatment durations, distinguishing specific antimanic effects from nonspecific sedative effects. • Lithium plus an antipsychotic and valproate plus an antipsychotic suggest greater efficacy or a more rapid onset of action than with these agents alone • Combination of divalproex plus an SSRI an effective strategy for management of breakthrough depression during maintenance of bipolar I disorder
2006	Alcohol use disorders	• 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 • Myth: Combining more than one treatment method has no advantage.
2006	Nicotine use dirorders	• 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
2006	Opioid use disorders	• In the management of withdrawal, non opioid medications like clonidine, benzodiazepines, NSAIDs or a combination of these. • Rapid detoxification: Naloxone in combination with other medications such as clonidine and benzodiazepines • Naltrexone with clonidine for rapid detoxification is safe and effective • Buprenorphine and naloxone combination utilized for agonist maintenance therapy
2007	Elderly anxiety disorders	• Benzodiazepines may be used to reduce the severity of anxiety, the need for rapid anxiolysis along with SSRIs • Beta blockers may be used as augmenting agents, especially when somatic symptoms of anxiety are prominent • Low dose of a tricyclic antidepressant could be used to treat insomnia associated with anxiety in patients who are receiving SSRI.
2007	Alzheimer's disease	• The use and combinations of pharmacological agents should be decided on a case-by-case basis.

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?	☐	☐
b. Thorough evaluation of diagnosis?	☐	☐
2. Evaluation of medication history:		
a. Efficacy of past medications documented/reviewed?	☐	☐
b. Reported side effects of past medications documented/reviewed?	☐	☐
c. Dose and duration of past monotherapy attempts documented/reviewed?	☐	☐
i. At least 21 days of continuous use at same dose? (Mood stabilizers and antipsychotics may require longer trials.)	☐	☐
ii. 2-to-3 monotherapy trials with drugs from different classes?	☐	☐
iii. Review of diagnosis after failure of several monotherapy trials?	☐	☐
3. Patient compliance:		
a. Review of patient compliance during medication trial(s) documented?	☐	☐
b. Patient involvement in reviewing treatment response and treatment options?	☐	☐
c. Review of simplicity of regimen and avoiding complicated regimen?	☐	☐
4. Evaluation of the current medication regimen:		
a. Rationale for each current medication reviewed?	☐	☐
b. Efficacy of each current medication reviewed?	☐	☐
c. OTC medications, herbal remedies, and illicit drugs reviewed?	☐	☐
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).	☐	☐
5. Review of medication changes:		
a. Total number of medications reduced before adding new one?	☐	☐
b. Only one medication changed at a time?	☐	☐
c. Medication changes completed? Old medication discontinued after new one at therapeutic level for sufficient period of time?	☐	☐
d. Cross-titrations used only with those medications for which this strategy is required?	☐	☐
6. Demonstrable need:		
a. Medications without clear benefit for target symptoms eliminated?	☐	☐
7. Combined and Augmented Pharmacotherapy:		
a. Justification for same-class polypharmacy clearly documented?	☐	☐
i. Specific targeting of different symptom clusters?	☐	☐
ii. Synergism in the drugs' mechanisms of action?	☐	☐
iii. Augmentation of partial treatment response or nonresponse to monotherapy?	☐	☐
iv. Improved risk/benefit ratio by reducing dosage and adverse effects for improved tolerability of one or both drugs?	☐	☐
b. Failed trials of monotherapy documented?	☐	☐
c. Efficacy data on strategically combined treatments reviewed?	☐	☐
8. Monitoring the risks of polypharmacy:		
a. Drug interactions reviewed?	☐	☐
b. Blood levels monitored periodically, especially with signs of toxicity or with medications likely to have drug interactions?	☐	☐
c. Monitoring of higher-risk combinations:		
i. More than one medication from the same class?	☐	☐
ii. More than two antipsychotic medications?	☐	☐
iii. Combinations with cumulative anticholinergic effects?	☐	☐
iv. Combinations with specific additive organ or system effects? (e.g., Cardiac, Renal, Hepatic, Respiratory, Gastrointestinal, Musculoskeletal)	☐	☐
9. Institutional mechanisms in place:		
a. Peer review	☐	☐
b. Automatic/forced drug interaction reviews	☐	☐
c. Supported access to medication information	☐	☐
d. Pharmacy consultation	☐	☐
e. Drug utilization review	☐	☐

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Author details

S. Haque Nizamie* and Sai Krishna Tikka

*Address all correspondence to: sh.nizamie@gmail.com

Central Institute of Psychiatry, Ranchi, India

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