Viewpoint Paper

Polypharmacy – is it here to stay

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Polypharmacy refers to the concurrent use of multiple medications with the same patient. In case of psychopharmacology, it refers to the use of two or more psychiatric medications in the same patient or the use of two or more medications to treat the same condition or the use of two or more medications of the same chemical class or prescribing more than two medications for the same indication even though these medications have the same or similar mechanisms of action and indication [1]. It is noteworthy for psychiatrists to realize that the numeric threshold in the definition of polypharmacy in psychiatry is imprecise and the use of multiple psychiatric medications while deemed to have probable negative consequences, may actually be an effective clinical intervention [2]. There has been an exponential rise in the use of polypharmacy in psychiatry. The reasons for this change are multi-pronged and include the fact that different medications targeting different receptors are now available and we are in an era of specific symptom-based psychopharmacology rather than one which is disorder based [3].

The National Association of State Mental Health Programme Directors (NASMHPD) classify psychiatric polypharmacy into various types – [4]

- **Same-class Polypharmacy:** the use of more than one medication of the same class. For example, using two different SSRIs to treat depression.
- **Multi-class Polypharmacy:** the use of full therapeutic doses of more than one medication from different classes for the same disorder / symptom-cluster. For example, use of Lithium and Olanzapine for the treatment of mania.
- **Adjunctive Polypharmacy:** where one medication is used to treat the sided effects of another medication. For example, Aripiprazole in Amisulpride induced hyperprolactinemia.
- **Augmentation Polypharmacy:** the use of one medication at lower dose with another medication at full dose. For example, low dose Haloperidol to augment effects of full dose Risperidone.
- **Total Polypharmacy:** the total count of medications used in a patient and is also referred to as the total drug load.

Factors leading to Psychiatric Polypharmacy

The factors that have led clinicians to prescribe multiple drugs in psychiatry is the understanding that a single medication is not enough to treat complex psychiatric disorders. Other reasons for prescribing multiple drugs are viz. to target different symptoms; to target two distinct psychiatric illnesses (example, ADHD and Depression); to address unremitting symptoms; and to preventively deal with sided effects [5]. Yet other reasons for multiple drug prescribing include geographical differences in psychotropic prescribing and differences in prescribing practices between psychiatrists in the same city [6]. One crucial factor that has contributed in polypharmacy includes greater patient emphasis on symptom reduction and the discriminatory exclusion of psychosocial treatments by psychiatrists, thereby, placing heavy clinical demands on psychopharmacology alone [7].

Scientific factors that have contributed to polypharmacy include the understanding of multiple neurotransmitters being involved in the causation of the same psychiatric disorder. Clinical issues where clinical judgement moves above the available theoretical diagnostic criteria leading to extensive overlapping diagnoses and thus, poly-nosology contributes polypharmacy [8]. A financial factor includes the economic emphasis and impact of pharmaceutical industries and heavily marketed medications that influences the demand on psychiatrists to prescribe multiple drugs [9]. Political factors where specific

conditions and specific drugs get FDA approvals for specific conditions can lead to multi-prescribing along with cultural factors in certain countries where patients have a large appetite for pharmacological treatments has also contributed to the phenomenon of polypharmacy [10]. This is coupled with patients who self-medicate and visit multiple doctors not informing one doctor about other as seen in clinical practice. Many psychiatrists prefer symptom-based prescribing and fear patient dissatisfaction leading to multiple drugs being prescribed in order to garner a hastened cure [11].

Financial reasons for polypharmacy in developing countries are health insurance schemes that do not cover psychiatric illnesses and where the patient is often a sole bread winner, thereby multiple drugs are prescribed in order to get the patient back to work and recovery as fast as possible. In the digital era, it is also prudent to know that well-informed patients often have poor knowledge, greater demands and higher expectations from the treatment they seek, putting pressure of the psychiatrist to put them on multiple mediations [12]. Sometimes, a heavy patient load compromising tie spent on each patient with lack of time for non-pharmacological therapies may resort to polypharmacy quick fixes that increases patient reliance on poly-drug treatment [13].

The Merits of Polypharmacy [14]

- It is useful in treating multiple psychiatric disorders together and comorbidities in the same psychiatric disorder. For example, management of depression and panic disorder or management of ADHD and enuresis.
- Polypharmacy results in multiple drugs being prescribed at lower to normal dosages rather than one drug at a higher dosage, which reduces side effects.
- Better disorder management when multiple drugs acting on multiple neurotransmitters are used, results in better symptoms recover and faster improvement.
- Polypharmacy may also provide faster relief where one group of medications may act earlier while waiting for the other medications to act in two-to-three weeks. For example, starting Clonazepam to alleviate anxiety while Escitalopram may take 7-10 days for full action.
- Judicious and rational polypharmacy can provide better symptom relief and disease management in patients that have been refractory so far.

Demerits of Polypharmacy [15]

- Psychiatrists need to be aware that polypharmacy may lead to over or under dosage of medications and at the same time cause cumulative toxicity due to multiple drugs having to undergo liver or renal clearance. This is very important in patients that have medical disorders and are medically compromised.
- Polypharmacy can also lead to medication combination errors (for example, 2 sedating medications may have additive effect) and non-compliance on the part of the patient where patients may skip one or more medications thinking that the others will act (for example, when on 4-5 medications patients sometimes on their own skip one or two medications either on their own or not having purchased all the drugs).
- Patients may also be on multiple medications for their medical conditions and clinicians must be aware when using polypharmacy of the medical side effects of psychiatric medication and the psychiatric side effects of medical drugs. This is important if the patient is on steroids, immunosuppressants and anti-infectious agents that may have psychiatric side effects.
- Polypharmacy results in increased total medication cost and financial burden on the patient along with the increase in total pill-count which negatively affects patient compliance.
- Some authorities believe that the practice of psychiatric polypharmacy is based more on educated clinical guess work rather than scientific evidence. There is a lack of randomized control trials of psychopharmacological polypharmacy so as to consider its use as evidence based.

Irrational Polypharmacy [16]

While most of the times, polypharmacy in psychiatry is based on the clinical expertise and scientific judgement of the practicing psychiatrist, there are times where it may be irrational and non-scientific and deserves special mention as below –

- Fear and laziness on the part of the treating psychiatrist resulting in aimlessly adding medications while not removing those which are unwanted, can result in drug tolerance and drug dependence to a particular class of drugs and cumulative toxicity with additive side effects.
- Faulty or sloppy diagnosis, for example, a patient with hallucinations may be treated as one having schizophrenia then actually the symptoms may be mood congruent and relate to depression. Proper detailed history taking and clinical mental status examination is a must a prior to considering polypharmacy.
- Botched or stuck cross titrations when switching drugs may cause worsening of the patient, resulting in the psychiatrist leaving both the drugs at same doses and/or adding a third drug, causing further drug-drug interactions and side effects.
- Blind adherence to certain clinical guidelines like the Physician's Desk Reference and following dosages mentioned there without clinical judgement can cause problems to the patient. The dosage in guidelines is just a guide as the name suggest and actual dosage needed by the patient must be based on clinical judgement of the psychiatrist.
- Inadequate knowledge of neurobiology and receptor pharmacology or lack of attention to the same, along with the need to rush to extract a cure can lead to irrational polypharmacy. Psychiatrists need to well versed in recent advances in psychopharmacology and neurobiology to consider polypharmacy.
- Improper examples and sources of knowledge like data presented in industry-sponsored seminars where speakers rather than giving expert opinion may promote the company's medication in indications that have not been well studied or approved resulting in naïve psychiatrists engaging in poorly planned polypharmacy.
- Many clinicians may have magical thinking and firm near-delusional belief that about their prescribing practices and what works in certain disorders, resulting in not wanting to change/upgrade while dealing with their own medieval scientific beliefs.

Clinical Issues in Polypharmacy

Polypharmacy is a complex skill and involves the art if prescribing which is clinically challenging yet rewarding. It is important that clinicians when using multiple drugs should also address compliance, have a dialogue with patients and relatives and psycho-educate them for the need for multiple drug treatments. It is also vital that periodic review of prescriptions, assessment of side effects and making changes where needed is carried out [17]. It is important in polypharmacy, that each prescribed drug should have clear indications, well defined therapeutic goals and must be evidence-based as far as possible. Patients must be informed about the same to enhance compliance and their reliance on polypharmacy. It is also crucial that psychosocial treatment like psychotherapy, family therapy and cognitive remediation be carried out hand in glove with multiple drug prescribing to further enhance the effects of drug therapy [18].

There is a need for proper clinical titration, sound treatment algorithms and well-defined protocols- that would be an effective way to reduce irrational multiple drug prescribing. An important clinical issue is when a patient on multiple drugs presents to a psychiatrist and he would want to change that prescription and prescribe his own set of multiple drug-combination. It is important that the certain drugs from the previous prescriptions be retained so that a comfortable switch can be made to one prescription to the other. Tapering off of medication must be done at a gradual rate with monitoring for withdrawal / rebounding symptoms. It is also wise that medications with similar half-lives are switched to enhance continuity in action.

If the switched schedule of medication too much discomfort, the patient must be instructed to return immediately to the previous dose until switch can happen again. It is also essential that during this drug-change / wash out, the patient's support system (family members / relatives) must be taken into

confidence to monitor patient safety, mood swings and any rare events that may occur as a result of polypharmacy [19].

Another worry for polypharmacy is psychiatric multiple drug prescribing by non-psychiatrists (physicians) which often goes unnoticed and unreported. There is also a tendency to prescribe psychotropics without a clear diagnosis resulting in anti-psychotics being prescribed to patients with depression and anti-depressants being prescribed to patients with schizophrenia when actually these must be augmenting psychiatric agents [20].

Conclusions

We are clearly in an era where polypharmacy is necessary and where monotherapy often provides for insufficient improvement. The dilemma is the number of overwhelming drug possibilities available and the need to be aware of the right permutations and combinations. This perplexing decision is left to the clinician where rational prescribing rather than risky trial and error should happen. There is also a lack of knowledge of drug-drug interaction, fear of changing drugs, prescription laziness and scientific misunderstanding of psychopharmacology.

While randomized controlled trials of polypharmacy are absent mini-experiments in a clinic drawing on wise drug selection and pharmacological decisions must be noted when successful in individual patients. Clinicians must regularly review scientific journals, clinical trial data, research on drug safety, latest neurobiological research and update their knowledge of drug interactions to enable them to become scientific yet judicious, rational polypharmacy users. The most important point is the decision whether to opt for multiple drugs or stick to monotherapy. Psychiatrists who prescribe multiple drugs often may see better results, may see side effects but have better clinical outcomes than patients on monotherapy alone. Thus, one must use polypharmacy judiciously and rationally for better patient care in the years to come.

Key Take Home Messages

- Psychiatric polypharmacy is needed in the modern era where psychiatric disorders have an underlying neurobiology with multiple neurotransmitters.
- There is a need for clinicians to practice psychiatric polypharmacy which is scientifically sound and ethically rational.
- The merits of psychiatric polypharmacy include multi-pronged treatment of psychiatric disorders, lower dosages of drugs and ensuing lower side effects and faster improvement in patients.
- The demerits of psychiatric polypharmacy include irrational combination of drugs of the same class, cumulative toxicity and additive side effects.
- Psychosocial treatments like psychotherapy, family psycho-education, family therapy and cognitive remediation must be started to further enhance the effects of psychiatric polypharmacy.
- Psychiatrists who prescribe multiple drugs often may see better results, may see side effects but have better clinical outcomes than patients on monotherapy alone.

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Acknowledgements – Nil
Source of Funding – Nil
Conflict of Interest – Nil