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Editor-in-Chief

The spectrum of
polypharmacy ranges
from the rational
to the irrational

Polypharmacy subtypes

The necessary, the reasonable, the ridiculous, and the hazardous

You've heard about the 2 certainties in life: death and taxes. In psychiatric practice with complex and chronic patients, there is a third certainty: polypharmacy. It ranges from thoughtful to indiscriminate and seems to be entrenched in clinical practice, possibly reflecting practitioners' desperation in trying to manage severely ill, treatment-resistant patients, usually in the absence of evidence-based guidelines.

I never fail to encounter polypharmacy in hospitals or clinics where I consult. I always wondered how the patient's doctor knew which drug was exerting a therapeutic effect or which drug was causing side effects (parkinsonism, akathisia, sedation, orthostasis, dizziness, headache, blurry vision, etc.). Over time, I came to categorize polypharmacy into 4 subtypes that span the spectrum from sensible to absurd. Here is my personal classification, which I trust that you, my readers, have witnessed as well.

Necessary polypharmacy. This variant of polypharmacy is evidence-based and proven in double-blind studies to be more effective than monotherapy. The most prominent example is adding an atypical antipsychotic to a mood stabilizer in bipolar mania. In fact, the superior efficacy of combination therapy in bipolar disorder is one of the oldest forms of rational polypharmacy, is supported by FDA trials, and is indicated whenever mood stabilizer monotherapy is not sufficient. For example, combining lithium and valproate is superior to either drug alone. Another example of FDA-approved combinations is combining small doses of an atypical antipsychotic to an antidepressant for treatment-resistant depression.

Reasonable polypharmacy. Although many of the combinations in this category are not FDA-approved, controlled studies support their use for suffering patients. Examples include:

- An atypical antipsychotic added to a selective serotonin reuptake inhibitor (SSRI) for obsessive-compulsive disorder (OCD) patients who do not improve on SSRI monotherapy.

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- Modafinil added to clozapine in patients who suffer substantial and persistent daytime sedation or somnolence.
- Combining 2 antidepressants for major depressive disorder patients who partially respond to 1 antidepressant.
- Combining a mood stabilizer with an antidepressant for bipolar depression to prevent mood switching.

Ridiculous polypharmacy. The sky is the limit to the variations and degrees of ridiculous polypharmacy, but the theme is the same: an absurd concoction of psychotropic drugs across several classes, often including multiple agents from 1 or several classes. Here are examples I have seen in patient records:

- Two atypicals, an anticholinergic, a mood stabilizer, an antidepressant, and 2 benzodiazepines.
- Three antipsychotics (2 atypicals and 1 typical), 2 antidepressants, 3 sedative/hypnotics, and an anticonvulsant for weight control.
- This one takes the cake: 6 antipsychotics (2 typicals and 4 atypicals), plus an anticholinergic, 3 mood stabilizers, 2 antidepressants, 2 sleeping pills, a hypoglycemic agent, 2 antihypertensives, and a statin.

Hazardous polypharmacy. In this category, serious medical complications, toxic effects, or death may occur because of careless combinations of drugs that may interact to produce dangerous kinetic interactions or exacerbate a pre-existing medical condition. Examples include:

- Combining 1 psychotropic with another that may inhibit its metabolism (eg, prescribing fluvoxamine to a severely psychotic patient who developed OCD while receiving clozapine). There have been several toxic reactions and even death because fluvoxamine inhibits cytochrome 1A2, which metabolizes clozapine, thus increasing clozapine blood level by 400% to 500%.
- Combining 2 injectable drugs for agitation that may cause a serious medical complication. An example would be injecting a benzodiazepine such as lorazepam in a patient receiving olanzapine IM, which can cause severe respiratory depression or death.
- Combining several drugs, each of which may prolong the QTc interval, resulting in syncope or torsade de pointes.

Psychopharmacology can relieve the terrible anguish of psychosis, depression, or anxiety, but it also can carry iatrogenic risks if it is not based on scientific evidence. The practice of psychopharmacology requires the fully integrated skills of medical and psychiatric training to maximize benefit while avoiding harm. It also requires basic arithmetic skills: to consider subtracting drugs, not only adding them!



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