

**PSYCHOTROPIC MEDICATION ACTION PLAN (PMAP)
A STATEWIDE PARTNERSHIP**

Psychotropic Polypharmacy

Ryan Kimmel, MD

Medical Director, Inpatient Psychiatry, UW Medical Center
Assistant Professor, UW Psychiatry and Behavioral Sciences

Robert Hilt, MD

Director, Partnership Access Line for Children Mental Health Consultation Services
Seattle Children's Hospital
Assistant Professor, UW Psychiatry and Behavioral Sciences

Jürgen Unützer, MD, MPH, MA

Chief of Psychiatry, UW Medical Center
Professor and Vice Chair, UW Psychiatry and Behavioral Sciences

Richard C. Veith, M.D.

Richard D. and Bernice E. Tutt Professor in the Neurosciences
Chair, UW Psychiatry and Behavioral Sciences

Every client deserves the opportunity to be tried on a lower risk regimen. A trial of a different regimen, with a clinical need to switch back, is not a failure. It documents that you tried. – Molly Finnerty, MD

Introduction:

Psychotropic polypharmacy is the use of more than one psychiatric medication by a patient. There are rare regimens wherein polypharmacy might result in an increased efficacy that potentially outweighs the increased risk, such as the benefit suggested in the STAR*D study for augmenting SSRI partial responders with another antidepressant class (Rush 2007). Some psychotropic polypharmacy regimens are necessary for patients with multiple psychiatric disorders. Cross-titration sometimes appropriately results in temporary polypharmacy. Some hospitalized patients acutely require multiple medications to rapidly address safety issues.

There is a quick limit to this “two is better than one” paradigm, however. Some polypharmacy regimens do not increase efficacy, but cause drug interactions and increase the total side effect burden. Providers and patients may be tempted to hold on to a medication that “used to work,” but is clearly not doing so now. Medications that are not tolerated at high doses, but not fully efficacious at low doses, are often augmented rather than replaced by a single agent trial.

Initial treatment failure is common. For example, most patients with depression will either not tolerate or not achieve full remission from an initial SSRI trial (Rush, Warden et al. 2009). Thus, it is not a surprise when patients and providers cling tightly to some semblance of success, even if sub-optimal. In this manner, old medications are maintained, and polypharmacy builds.

Medication dosing, like polypharmacy, is a complex issue. Whereas, the data on the benefits of pushing high dose SSRIs for refractory depression may be debatable (Adli, Baethge et al. 2005), high dosing of SSRIs for Obsessive Compulsive Disorder is a more accepted strategy (Pampaloni, Sivakumaran et al. 2010). Genetic variations can influence medication plasma concentrations and impact efficacy (Lenze, Goate et al. 2010). However, regimens that exceed the usual dosing range are increasingly common and have been identified as a quality concern by the Washington State DSHS. For most medications and most patients, the effectiveness of a medication plateaus at the upper range of the FDA recommended dosing. This has been demonstrated for antipsychotics (Davis and Chen 2004) and antidepressants (Hansen, Moore et al. 2009). High doses of medications are associated with poor medication adherence and side effects. For some patients, poor adherence leads to increasing regimen complexity, which leads back to poor adherence.

Before patients find themselves in a position where they are having minimal success and maximal side effects on a complex regimen, it might be useful to identify common polypharmacy strategies that lack broad evidence of efficacy, but do have evidence of toxicity. Toward, this goal, the Washington State Mental Health Council, the Department of Social & Health Services' Medicaid Purchasing Administration, and the University of Washington Department of Psychiatry have identified the following indicators:

- Antipsychotic dosing above the FDA approved maximum.
- The concurrent use of two or more antipsychotics for longer than 60+ days.
- Percent of patients with a current antipsychotic gap of >7 days.
- The concurrent use of five or more psychotropics.
- Percent of patients with an antipsychotic possession ratio >90%.

There are certainly rare, outlier patients, and limits to what is known from current scientific data. The authors' aims, however, are to identify the logic prescribers might employ to justify specific polypharmacy regimens, discuss the data on the efficacy of such regimens, and highlight the health risks to the patients.

Medication Classes:

1. Antipsychotics

For schizophrenia, there is an oft-speculated idea that combining a high-potency (high dopamine blockade) atypical with a low-potency atypical will create a "super atypical." For example, risperidone augmented with quetiapine is a strategy arrived at independently by a myriad of prescribers. Unfortunately for refractory psychotic patients, there is no evidence to support the concept of a "super atypical."

Despite the lack of evidence or consensus recommendation, the incidence of antipsychotic polypharmacy is rising (Mojtabai and Olfson 2010). Antipsychotic polypharmacy is associated with a higher risk of diabetes and a higher rate of the broader metabolic syndrome (Citrome, Jaffe et al. 2004; Correll, Frederickson et al. 2007). The data on antipsychotic dosing above FDA recommendations suggests similar issues, with no increased efficacy (Davis and Chen 2004), but with impairments noted in cognitive functioning (Kawai, Yamakawa et al. 2006), for example.

For schizophrenic patients seemingly refractory to everything, clozapine augmentation strategies have been tried. The evidence, as one would expect in such an ill patient population, has been mixed. For example, there are conflicting results for aripiprazole augmentation of clozapine (Chang, Ahn et al. 2008; Barbui, Accordini et al. 2011; Muscatello, Bruno et al. 2011), though this combination may not show the same additive metabolic side effect issues as other antipsychotic combinations.

While augmentation of SSRIs with certain antipsychotics may show benefit in such disorders as depression (Komossa, Depping et al. 2010) and OCD (Bloch, Landeros-

Weisenberger et al. 2006), antipsychotics may be too broadly used in disorders where the evidence is narrower, such as borderline personality disorder. Antipsychotics demonstrate a small effect size for a very narrow symptom cluster in borderline personality disorder (Ingenhoven and Duivenvoorden 2011). Despite this, polypharmacy in borderline personality disorder has increasingly become the norm, specifically with increased use of mood stabilizers and antipsychotics (Pascual, Martin-Blanco et al. 2010). Attention to personality and coping styles in these patients might direct interventions away from polypharmacy and towards an efficacious combination of a medication and psychotherapy (Linehan, McDavid et al. 2008).

The idea of simplifying an antipsychotic medication regimen in a stable schizophrenic patient creates anxiety in the patient, their family, and their prescriber. There are two studies on switching schizophrenics from antipsychotic polypharmacy to monotherapy. In an open label study of 44 patients, over half remained stable, 23% showed improvement, and 23% did worse (Suzuki, Uchida et al. 2004). In a more recent, randomized trial of 127 schizophrenics, two-thirds of patients successfully switched to monotherapy. Moreover, those on monotherapy had a 0.8 BMI improvement compared to those who remained on antipsychotic polypharmacy (Essock, Schooler et al. 2011).

2. Mood Stabilizers:

Mood stabilizers are often under-dosed. In the case of acute mania, for example, divalproex sodium has an established therapeutic blood level range, but also a linear-response curve within that range. In acute mania, a divalproex blood level of 94 is significantly more effective than a blood level of 75 (Allen, Hirschfeld et al. 2006).

During hospitalization for acute mania, it is common practice for a mood stabilizer and an antipsychotic to be initiated simultaneously. This is driven by the not-unreasonable impulse to improve the patient's safety quickly. However, these polypharmacy regimens are not always simplified when the patient is again euthymic. While the efficacy for traditional mood stabilizers for long-term maintenance is relatively well established, the data on the use of atypical antipsychotics for long-term bipolar maintenance are in its relatively infancy and there are instances where reputation exceeds evidence (Tsai, Rosenlicht et al. 2011). When acute mania has resolved and it is time to organize a regimen for long-term bipolar maintenance, it is appropriate to try a single mood stabilizer first.

Bipolar patients tend to spend much more time depressed than manic (Judd, Akiskal et al. 2002). Unfortunately, there are far more medications that show efficacy for acute mania than for acute bipolar depression. In fact, the only two medications that are FDA approved for acute bipolar depression are quetiapine and the fluoxetine/olanzapine formulation. Bipolar disorder is cyclical and with each new mood state, providers are tempted to add a new medication, with removal of ineffective medications delayed while awaiting an indeterminate period of euthymia.

3. Antidepressants:

There is some variety among antidepressants within the same class. Though it is impossible to predict who will respond to which, there are certainly depressed patients who fail citalopram, yet respond to sertraline, for example (Rush, Trivedi et al. 2006). There is not, however, evidence to support the simultaneous use of two SSRIs, two SNRIs, or an SSRI+SNRI combination. SNRIs have, by definition, a SRI component. Most, in fact, are more robust SRIs than NRIs (Sopko, Ehret et al. 2008). Thus, augmenting an SSRI with an SNRI, or vice versa, makes little sense. By switching from SSRI monotherapy to SNRI monotherapy, one is, in essence, already augmenting.

There is little data supporting the efficacy of using three antidepressants simultaneously. Practically speaking, there are very few patients who have tried all of the monotherapy and augmentation strategies that have shown some data on efficacy in refractory depression. That is, there are very few patients who have failed SSRIs, SNRIs, mirtazapine, bupropion, buspirone augmentation, lithium augmentation, liothyronine augmentation, TCAs, MAOIs, antipsychotic augmentation, cognitive behavioral therapy, and ECT, to name a few. Moreover, when a patient is on three antidepressants, it is difficult to track which medication is contributing to a partial response and which medication is contributing only to the side effect burden.

Though the utility of high-dose antidepressants in depression is debatable, dose increases are often preceded by poor medication adherence. Thus, medication noncompliance masquerades as poor efficacy (Muzina, Malone et al. 2011).

4. Stimulants:

While the efficacy for various stimulants and non-stimulants for ADHD varies widely (Faraone and Glatt 2010), there are no controlled data on combining multiple stimulants, or for using stimulants above FDA dosing recommendations. Similarly, while there is limited evidence on the off-label use of stimulants in depression (Candy, Jones et al. 2008) and cancer-related fatigue (Minton, Richardson et al. 2010), for example, these studies do not recommend dosing beyond recommendations in the FDA-approved, ADHD range. There is, however, evidence that stimulants carry a risk of cardiac toxicity and rare psychiatric side effects.

Clinical Recommendations:

1. Treatment with a single psychotropic medication, with adequate dose and duration, is the first-line approach.
2. Avoid complex regimens in patients whose character structure would suggest that they would respond better to psychosocial treatments.
3. Nonpharmacologic interventions, such as psychotherapy techniques showing benefit for specific diagnoses, should be considered before polypharmacy.

4. Physicians prescribing multiple psychotropics, or psychotropics above recommended dosing, should engage their patients in a conversation about the risks of the regimen, and the benefits of simplifying the regimen once the patient is stable.
5. Physicians who find themselves prescribing in a manner outside of the “quality indicators” could proactively consider a second opinion.
6. Gradual medication tapers are recommended when simplifying regimens.
7. Psychoeducation for the patient, their families, and their support network will improve a provider’s ability to track the effects of medication changes.
8. Rating scales filled out by the patient can be especially helpful during medication changes. For example, quick rating scales to monitor symptoms and medication compliance can be a useful aid for guiding clinical decision making (Trivedi 2009).
9. When considering initiating or continuing a polypharmacy regimen, avoid combining medications from the same class, avoid combining medications with the same mechanism of action, and avoid adding a medication without a clear indication or target symptom that can be easily tracked.

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