New York State Office of Mental Health

Quality Concerns in Psychotropic Prescribing: Reducing Psychotropic Polypharmacy

Reference Guide

PSYKES

Quality Concerns in Psychotropic Prescribing: Reducing Psychotropic Polypharmacy

In 2007, the NYS Office of Mental Health convened a Scientific Advisory Committee of national experts in psychopharmacology. Six workgroups (schizophrenia, depression, bipolar disorder, older adults, youth, and women) identified approximately 80 quality concerns in psychotropic prescribing that are common, costly, and measurable. This clinical module provides information on the quality domain of polypharmacy, including an overview of the evidence base and definitions of each indicator.

- ***Client focus:*** Clients who are prescribed multiple psychotropic medications
- ***Project goal:*** Simplification of medication regimen if clinically feasible following clinical evaluation, for each client prescribed polypharmacy
- ***Definition of polypharmacy:*** A medication regimen that includes one or more of the following for longer than 90 days: 2 or more antipsychotics, 2 antidepressants from the same class or 3 antidepressants from all classes, 4 or more psychotropic medications in adults, or 3 or more psychotropic medications in youth

Brief Definitions

PSYCKES Polypharmacy Indicators	
Antipsychotic polypharmacy of two or more agents [2AP]	The percentage of consumers of all ages on two or more antipsychotics for longer than 90 days, among those on at least 1 antipsychotic for longer than 90 days
Antipsychotic polypharmacy of three or more agents [3AP]	The percentage of consumers of all ages on three or more antipsychotics for longer than 90 days, among those on at least 1 antipsychotic for longer than 90 days
Antidepressant polypharmacy of two or more agents in the same subclass [2AD]	The percentage of consumers of all ages on two or more antidepressants in the same subclass for longer than 90 days, among those on at least 1 antidepressant for longer than 90 days
Antidepressant polypharmacy of three or more agents [3AD]	The percentage of consumers of all ages on three or more antidepressants for longer than 90 days, among those on at least 1 antidepressant for longer than 90 days
Psychotropic polypharmacy in adults (four or more) [4PP(A)]	The percentage of consumers eighteen years and older on four or more psychotropics for longer than 90 days, among those on at least 1 psychotropic for longer than 90 days (in adults)
Psychotropic polypharmacy in youth (three or more) [3PP(Y)]	The percentage of consumers younger than eighteen years old on three or more psychotropics for longer than 90 days, among those on at least 1 psychotropic for longer than 90 days
Polypharmacy summary	The percentage of consumers meeting criteria for any of the polypharmacy indicators, among those on at least 1 psychotropic for longer than 90 days

Scope of the Problem

Psychotropic polypharmacy refers to the prescription of more than one mental health medication for a consumer. The PSYCKES polypharmacy indicator set identifies consumers who are taking psychotropic medication combinations that may pose a health risk. The prescribing practices targeted are: a) the practice of combining two or more psychotropic medications to treat the same condition, b) the use of two or more drugs in the same chemical class or with similar pharmacologic properties or c) the concurrent use of 4 or more psychotropic medications of any type in adults, or 3 or more in children. The project addresses longer term prescription of multiple medications for 3 months or longer. Polypharmacy was identified as a quality concern by the PSYCKES Scientific Advisory Committee, an expert panel convened by OMH [1].

Use of more than one medication to treat an individual with a psychiatric disorder has increased in the United States during the past decade. In a national survey of outpatient visits by adults to psychiatrists, prescription of 2 or more psychotropic agents increased from 43% to 60% between 1996 and 2006, and the prescription of 3 or more agents increased from 17% to 33% [2]. Two-thirds of individuals with depression have an incomplete or poor response to antidepressant medications, and are often treated with multiple psychotropics [3]. New York State 2010 Medicaid claims data for 45,390 individuals served in OMH-licensed programs on long-term medications showed that 13.5% were prescribed two or more antipsychotics for at least 3 months. Data on polypharmacy show that 21.1%% of children in OMH-licensed programs are receiving three or more psychiatric medications, and 15.2% of adults in those programs are receiving four or more agents.

Polypharmacy is especially worrisome in children and adolescents with psychiatric or behavioral disorders. There are a limited number of clinical trials in this population, and very little research on the risks of psychotropic medications in the developing brain. As a result, far fewer medications have been approved for use in children and adolescents by the Food and Drug Administration. Patterns of polypharmacy in youth suggest that youth on more than 1 medication are likely to be taking one which increases the risk of suicidal thinking, such as antidepressants, mood stabilizers, and atypical antipsychotics. Despite these risk concerns, the trend toward increased polypharmacy seen in adults appears to be present in children and adolescents. In a national study of office-based psychotropic prescription in children and adolescents with a psychiatric diagnosis, the rate of polypharmacy increased from 22% to 32% over 12 years [4]. In a recent study of Medicaid claims in one state, 38% of youth on any psychotropic medication were prescribed more than one drug [5].

There are a number of reasons why a prescriber may combine psychotropic medications within the same class or across classes. When switching from one drug to another, both medications may be prescribed at the same time, as the dose of one decreases while the other increases (cross-titration). Inadequate treatment response to monotherapy can be addressed by adding a second medication. Side effect problems can be managed by adding a second medication to treat the side effects. Alternately, the dose of the offending medication can be lowered, and a second medication with a different side effect profile can be added to bolster response. Multiple psychotropics may be prescribed for a short time during and immediately after a hospitalization. More than one medication may be needed for some people with multiple psychiatric disorders. A consumer may be prescribed additional medications considered psychotropics for the treatment of medical illnesses, for example chronic pain conditions or epilepsy. Many consumers are also prescribed mood stabilizers, stimulants or antianxiety medications, and although these can be very helpful, they can in combination lead to more adverse drug interactions and increase the overall side effect burden.

Quality Concerns in Polypharmacy

There is minimal scientific evidence that combining psychotropics is effective. Antipsychotic polypharmacy has been examined primarily through studies on the co-prescription of clozapine and other antipsychotics for clients who do not have adequate symptom reduction with clozapine alone; the results are mixed [6, 7]. The majority of antipsychotic combination therapy in clinical practice involves combination of second generation antipsychotics, for which there is very little supporting scientific data. There are many studies noting the effectiveness of combining antidepressants with other medications, such as lithium or thyroid hormone, but only recently have researchers begun to examine the effectiveness of combining multiple antidepressants [1]. Despite the absence of evidence, surveys indicate that prescribers frequently combine antidepressant medications [8].

Polypharmacy has serious potential risks. Polypharmacy increases the side effect burden for consumers, both acutely and over the long term. Antipsychotic polypharmacy places the consumer at higher risk for extrapyramidal neurologic side effects [9]. Recent studies in people taking two second generation antipsychotics have also documented an increased risk for elevated blood sugar and new onset diabetes with life threatening complications including diabetic ketoacidosis [7, 10]. In a recent survey of outpatient prescribing practices, metabolic syndrome was significantly more common in consumers prescribed more than one antipsychotic concurrently [11]. Other side effects likely to be more common in consumers prescribed multiple agents include sedation, cognitive deficits, dizziness, low blood pressure, endocrine dysfunction, and diminished sex drive and performance. There is a higher risk for adverse drug-drug interactions. Adherence decreases, with consequent risk of relapse. People prescribed polypharmacy may be receiving higher than necessary total doses within a drug class. It can be difficult to determine which agent may be helping the client and which may be causing toxicity. Treatment costs are higher, without any evidence of clinical benefit. Several studies have found an increased risk of mortality in patients receiving long term therapy with multiple psychotropics [12].

There is a paucity of published guidance for clinicians regarding simplification of medication regimens designed to reduce polypharmacy. One recent study looked at 44 consumers taking 2 or more antipsychotics, and followed their clinical status as their medication regimen was simplified to a single antipsychotic. The outcomes for consumers suggest that the majority can be successfully switched to monotherapy [13].

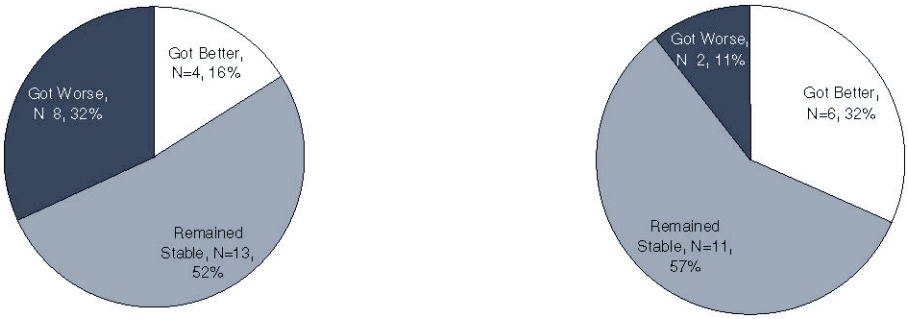

Figure 1. Clinical Outcomes Following Switch to Monotherapy (Suzuki et al., 2004)

Clinical Recommendations for Reducing Psychotropic Polypharmacy

1. **Treatment with a single psychotropic medication (monotherapy)** is the first-line treatment approach. Prescribers should ensure that the **dose and duration of monotherapy trials are adequate,** and consistent with evidence-based guidelines.
2. **Nonpharmacologic therapies**, for instance cognitive behavioral therapy for insomnia, anxiety, or depression, are well-researched and effective for management of symptoms. Psychosocial interventions should be considered as an alternative strategy to polypharmacy for symptom control and improved wellbeing.
3. Consumers who are prescribed multiple psychotropics within or across classes should be **engaged by their prescribers in a conversation** about the risks associated with their regimen, and the benefits of making a change. Reducing polypharmacy should be considered if clinically appropriate.
4. For consumers receiving more than one agent from the same class, **periodic efforts should be made to taper off medications** and to streamline the pharmacology once the consumer is doing well.
5. **Gradual medication tapers are recommended** when discontinuing medications. Medication changes are tolerated best by consumers when the changes proceed slowly. A common clinical practice is to change a medication by no more than 1/3 of the current dose, no more frequently than every 2-3 weeks.
6. **Psychoeducation** in varied formats should be available to all consumers. Brochures, scientific summaries, information sessions, and ongoing medication education groups can be helpful in providing information for consumers and promote dialogue with prescribers.
7. Consumers and families will benefit from **supportive services** from the clinic during periods of medication change. These services may include frequent check-in calls with the clinic nurse, increased appointment frequency with the prescriber and therapist, medication groups with other consumers, and psychoeducation about side effects or symptoms likely to be experienced. Specific interventions for management of changes in wellbeing may be developed by the clinical staff to **provide clients with tools** to use during the change.
8. **Rating scales** filled out by the client can be very helpful during medication changes. Rating scales can educate consumers in understanding and observing symptom constellations over time; and provide clinicians with accurate longitudinal information about the effect of medication change or discontinuation on symptoms and function.
9. If, after careful review, the prescriber and consumer decide to begin or continue polypharmacy:
    a. Combining **medication** from the same class, for example antipsychotics, should only be considered **after a series of failed monotherapy trials**.
    b. There should be a **clear indication and clear target symptoms** identified for each medication prescribed.
    c. When adding a second medication, consider an **agent with a different mechanism of action**.

Annotated Bibliography for Reducing Polypharmacy in Adults and Youth

These papers have been selected and briefly summarized to provide clinicians and CQI teams with key evidence from the scientific literature which may be helpful in informing clinical practice and working with clients to reduce their health risks from psychotropic medications. The scientific summaries located on the PSYCKES website provide more in-depth information and critical review of important scientific articles.

1. **Suzuki T, Uchida H, Tanaka KF et al. Revising polypharmacy to a single antipsychotic regimen for patients with chronic schizophrenia.** *International Journal of Neuropsychopharmacology* 2004; 7:133-142.

There are many studies which document the rising rates of antipsychotic polypharmacy and adverse metabolic effects in people who take even a single agent. However there is very little evidence on outcome when patients are converted to monotherapy. This study, which is also on the PSYCKES website as a scientific summary, provides some answers to the question of outcome. This is a naturalistic prospective study of 44 patients with schizophrenia who had been clinically stable on the current regimen for 6 months, and did not have a history of substance use, mental retardation, or head injury. Most antipsychotic combinations included high- and low-potency FGAs. The study included both inpatients and outpatients. Of note, the study was conducted in 1999 in Japan, when the only atypical antipsychotic available was risperidone (Risperdal).

- Three quarters of patients either got better (23%) or remained stable (55%).
- Average chlorpromazine equivalent dose dropped from 1171 mg to 952 mg.
- For those patients who had a clinical deterioration, time to relapse was 10 weeks.
- Interestingly, mean GAF of 35 did not change.

2. **Kawai N, Yamakawa Y, Baba Y et al. High-dose of multiple antipsychotics and cognitive function in schizophrenia: The effect of dose-reduction.** *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2006: vol 30, p1009-1014.

This study was completed in Japan with 17 patients with schizophrenia on 2 FGAs with a total dose of at least 1400 mg chlorpromazine (CPZ) equivalents, who had been stable for one year. There were 6 control patients whose medications were not changed. For clients taking less than 2000mg CPZ equivalents the target dose was 1000mg CPZ equivalents; for clients taking more than 2000mg CPZ equivalents the target was 1500 mg CPZ equivalents. Dose reductions began with the drug prescribed at the lowest dose, and occurred weekly by 50mg CPZ equivalents. Pre- and post intervention neurocognitive testing (Wisconsin Card Sorting Test (WCST), Continuous Performance Test (CPT)) and PANSS were collected.

- No patient had a serious decompensation.
- **Average number of antipsychotics per patient decreased from 3.5 to 2**, and CPZ dose equivalents decreased by a mean of 42%
- Cognitive function after dose reduction: On the WCST the perseverative errors decreased and correct answers increased substantially. This improvement correlated with improvement in the negative symptom subscale of the PANSS. There was no change in WCST or CPT in the control group.
- Improvement in WCST did not correlate with magnitude of reduction in dose.
- There was no change in the CPT.

3. **Goldberg JF, Brooks JO, Kurita K et al. Depressive Illness Burden Associated with Complex Polypharmacy in Patients With Bipolar Disorder: Findings From the STEP-BD.** *Journal of Clinical Psychiatry* 70(2):155-162, 2009.

There is the most evidence that the use of two medications can improve outcomes in bipolar disorder. However patients with bipolar disorder often receive 4 or more medications. This naturalistic observational study from the STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) provides some insight on factors associated with clients with bipolar disorder who are prescribed 4 or more psychotropics. There were 4035 consumers age 15 or older enrolled in this part of the study; two thirds of these had Bipolar I Disorder. The 7 core medication groups studied were: lithium, divalproex, carbamazepine, lamotrigine, other anticonvulsants without thymoleptic properties (topiramate, neurontin and others), antipsychotics and antidepressants. Use of other medications such as benzodiazepines was not included in this analysis.

- 12% of subjects were on none of these medications; 21% were on 1, 28% took 2, 22% took 3, and 18% took >3.
- Subjects taking less than 4 medications were more likely to be taking a proven mood stabilizer: lithium, divalproex, carbamazepine or lamotrigine.
- Antidepressants were associated with the largest effect size (0.78) leading to treatment with 4 or more medications.
- The subject profile associated with the greatest risk of taking ≥4 psychotropics included 1) receiving an atypical antipsychotic, 2) 6 or more depressive episodes, 3) history of a suicide attempt.
- Clinical parameters which did NOT affect risk for polypharmacy included 1) a history of psychosis, 2) rapid cycling, 3) number of hospitalizations, 4) age at onset, 5) substance abuse, 6) current state at enrollment (euthymic vs. not euthymic) and 7) bipolar I vs. bipolar II subtype.

4. **McIntyre RS, Jerrell JM. Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents.** *Archives of Pediatric and Adolescent Medicine* 162(10):929-935, 2008.

This rich study highlights the increased effects of both antipsychotic polypharmacy as well as polypharmacy involving antipsychotics plus another class of medication on cardiovascular and metabolic illness in youth under 18. It is designed as a retrospective cohort study using Medicaid data in a single state (SC), and compares the incidence/prevalence of metabolic, cardiovascular, and cerebrovascular events in a group of youths treated with antipsychotics (n=4140) to a random sample of youth (n=4500) without antipsychotic exposure over a 10 year period. The study compared risks between the exposed and unexposed groups, and then looked at which factors increased the risk of cardiometabolic health problems in both groups. Potential factors examined including gender, ethnicity, age, antipsychotic polypharmacy, and other drug classes prescribed concomitantly with the antipsychotic. Preexisting cardiovascular, cerebrovascular, and metabolic disorders were factored out.

- 42% of youth received antipsychotic polypharmacy.
- The antipsychotic-treated cohort had higher prevalence of obesity (OR 2.13), Type 2 diabetes (OR 3.23), and cardiovascular conditions (OR 2.70). The control sample, interestingly, had a higher prevalence of dyslipidemia (OR 3.01) and hypertension (OR 2.35).
- Odds of obesity and/or weight gain were greatest for youth receiving antipsychotic polypharmacy (OR 2.28), polypharmacy including mood stabilizers (OR 1.78), polypharmacy including high risk antidepressants (amitriptyline, nortriptyline,

mirtazapine, and paroxetine) (OR 1.66). Female gender (OR 1.75), and age ≥13 (OR 1.34) were also significant.
- The odds of developing Type 2 diabetes were higher for youth on antipsychotic polypharmacy (OR 2.36), for girls (OR 1.79), and youth ≥ 13 (OR 1.52).
- The mean age of initiation of antipsychotic treatment was 11.4; the mean age of onset of incident Type 2 diabetes was 13.8. Youth taking aripiprazole (Abilify), compared to other psychotropics had significantly longer time to diagnosis of DM (OR 35.92).
- Odds of dyslipidemia were higher for antipsychotic polypharmacy (OR 5.26), girls (OR 2.08) and youth ≥ 13.
- Hypertension was unrelated to which antipsychotic was used.
- Incident cardiovascular conditions were more likely with the use of haloperidol (Haldol) (OR 4.34) and multiple antipsychotics (OR 1.57).

5. **Blader JC, Schooler NR, Jensen PR, Pliszka SR, Kafantaris V. Adjunctive Divalproex Versus Placebo for Children With ADHD and Aggression Refractory to Stimulant Monotherapy.** *American Journal of Psychiatry* 2009; vol 166, p1392-1401.

This interesting study provides evidence regarding polypharmacy in youth with ADHD who have aggressive behaviors. The study demonstrates that aggression resolves in a substantial proportion of youth with ADHD when the stimulant dose is titrated to maximum benefit, thus avoiding polypharmacy to treat potentially dangerous symptoms. It also proposes that divalproex (Depakote) may be helpful for aggressive symptoms which do not respond to stimulant optimization. 82 children from 6-13 years with ADHD and comorbid conduct or oppositional-defiant disorder and behaviors were at least moderate in severity. Children with MDD, Bipolar, Tourette's, PDD and mental retardation were excluded. The stimulant optimization lead in phase involved use of triphasic methylphenidate (Concerta) to 90 mg, biphasic methylphenidate (Metadate) to 60 mg, or Adderall SR to 35 mg titrated to resolution of both ADHD and behavioral symptoms. All children had concurrent behaviorally-oriented psychosocial treatment during this phase. Children who continued to have aggressive behaviors after stimulant optimization proceeded on to the divalproex vs. placebo phase of the trial.

- 50% (n=31) of children had clinically significant resolution of aggression with stimulant titration. 30 children continued on the divalproex phase.
- 57% of the children (n=8 of 14) taking an average dose of 567 mg (68 mg/liter blood level) of divalproex reached remission vs. 15% (n=2/13)of children on placebo. Note that the low numbers of children in this phase of the study limit generalization.

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