Quality Concerns in Psychotropic Prescribing: Reducing the Use of Higher than Recommended Doses of Psychotropic Medications

Reference Guide
Quality Concerns in Psychotropic Prescribing: Reducing the Use of Higher than Recommended Doses of Psychotropic Medications

- **Client focus**: Clients prescribed doses of psychotropic medications at doses higher than recommended
- **Project goal**: Reduction of medication dose if clinically feasible following clinical evaluation, for each client receiving psychotropics at higher than recommended doses
- **Medication classes included**: Antipsychotics, antidepressants, mood stabilizers, anxiolytics, and stimulants

**Brief Description**

<table>
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<tr>
<th>PSYCKES Dose Indicators</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Antipsychotics [DoseAP]</td>
<td>The percentage of consumers on antipsychotics in the past 35 days with evidence of a dose higher than the recommended maximum</td>
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<tr>
<td>Antidepressants [DoseAD]</td>
<td>The percentage of consumers on antidepressants in the past 35 days with evidence of a dose higher than the recommended maximum</td>
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<tr>
<td>Anxiolytic/Hypnotic [DoseANX]</td>
<td>The percentage of consumers on anxiolytics/hypnotics in the past 35 days with evidence of a dose higher than the recommended maximum</td>
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<tr>
<td>Mood Stabilizer [DoseMS]</td>
<td>The percentage of consumers on mood stabilizers in the past 35 days with evidence of a dose higher than the recommended maximum</td>
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<td>ADHD Medications [DoseADHD]</td>
<td>The percentage of consumers on ADHD medications in the past 35 days with evidence of a dose higher than the recommended maximum</td>
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<tr>
<td>Dose summary</td>
<td>The percentage of consumers meeting criteria for any of the dose indicators, among those on at least 1 psychotropic in the past 35 days</td>
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**Scope of the Problem**

The PSYCKES Dose indicator set focuses on individuals who are prescribed psychotropic medications at higher than recommended doses. New York State (NYS) 2010 Medicaid data demonstrate that 9.1% of consumers on psychotropic medications who are served by OMH-licensed programs are on higher than recommended doses. The Scientific Advisory Committee convened by NYS OMH identified dosages at higher than the recommended range in all classes of psychotropics as a significant quality concern for mental health and primary care prescribers [1]. The scientific literature has validated high doses of psychotropic medications as a health concern.
The most effective and most tolerable dose of medication varies for any given individual. Pharmacokinetics (how the body processes the medication) and pharmacodynamics (how the medication affects the body and brain) both vary individually and with age. Normal genetic variations related to both the drug target (i.e. a drug receptor) and drug metabolism [2-4] influence the dose at which a drug may produce the desired therapeutic effects or cause toxicity. Consequently, clients with similar symptoms may respond to very different doses. The Food and Drug Administration approval process includes determination of the lowest dose at which a medication is effective as well as the maximum dose likely to produce clinical improvement without serious or dangerous side effects. Some medications have different dose recommendations depending on the psychiatric condition for which the medication is prescribed. For example, SSRI antidepressants for Obsessive-Compulsive Disorder may be prescribed at higher doses than for depression or anxiety. The approved dose range for a drug as specified by the FDA approval accommodates individual variation in optimum dose for various uses of the medication. Some mood stabilizers and tricyclic antidepressants have therapeutic serum levels which guide dosing; the vast majority of clients taking these classes of medication reach a therapeutic blood level within the FDA approved dose range. For most psychotropic medications, the effectiveness of a medication does not increase proportionally to increases in dose.

Prescribers may prescribe psychotropic medications at higher than recommended doses for a number of clinical reasons. A client may have experienced a partial remission of symptoms without significant side effects at the upper limit of approved dosing, and in collaboration with the prescriber prefers to continue upward medication titration. Clients with poor response to the usual medication doses may receive higher doses of medication in an attempt to reduce their symptoms and improve function. Higher doses of medication may be used to attempt to dampen violent thoughts or behaviors toward self or others. Medication blood levels in individuals with rapid metabolism may be at the lower range of effectiveness at high doses despite documented adherence. A client may prefer the subjective sense of wellbeing obtained at a higher dose of medication, and may be willing, for instance, to trade in long term risks for symptom reduction.

Quality Concerns in Higher than Recommended Doses
An extensive series of studies conducted over a number of decades consistently demonstrates that doses higher than recommended are not generally associated with improved response. As early as 1955, higher doses of chlorpromazine were associated with decreased efficacy and increased neurologic adverse effects [5]. Rapid titration to high doses (“rapid neuroleptization”) was once common in acute treatment of psychosis with first-generation antipsychotics despite the absence of controlled trials demonstrating benefit. A bell-shaped dose-response curve apparent in both dosing and blood level studies of antipsychotics suggests diminished clinical response at both low and high doses [6]. More recent studies of second-generation antipsychotics have suggested a lack of increased benefit at high doses [7-9]. Despite decades of evidence that high doses of antipsychotics are more toxic and less effective than moderate doses, providers continue to prescribe high doses for a significant group of consumers. Dose-effectiveness studies involving psychotropics have shown that 40% of consumers received antipsychotic doses higher than recommended by the Patient Outcomes Research Team (PORT) without any increased benefit [10-12]. Higher doses of antidepressants are not associated with higher rates of clinically meaningful improvement [13]. High dosing is often associated with treatment non-response; clients who are least likely to respond to medications are often on the highest doses, and high doses are rarely reduced when there has been no clinical improvement.
Higher than recommended doses of psychotropics place the consumer at increased risk for adverse outcomes. One of the key barriers to recovery for consumers with psychiatric illnesses is poor medication adherence [14]. High doses of medication have been associated with decreased adherence, and increases in side effects at high doses are connected to increased dropout rates. Cognitive function can be impaired at high doses of antipsychotics [15] with evidence that cognitive function improves when the dose is lowered [16]. There has been some evidence linking high doses of antipsychotics to an even greater risk of metabolic syndrome and cardiovascular disease and consequent morbidity and mortality for clients [17,18].

Research suggests that children, youth and the elderly are particularly vulnerable to adverse effects of psychotropic medication. In children, high doses of stimulants can cause insomnia and appetite suppression [19,20]. Elderly consumers on high-dose psychotropics had a nearly 3-fold increase in falls [21]. In some studies the prevalence of weight gain and extrapyramidal symptoms are higher in youth than in adults [22] and side effects can be dose-dependent. In summary, the scientific evidence suggests that high doses of psychotropics are not more effective than moderate doses, and may cause more adverse outcomes.

Clinical Recommendations for Reducing Higher than Recommended Doses of Psychotropic Medications

1. Consumers who are prescribed higher than recommended doses of psychotropics should be engaged by their prescribers in a conversation about the risks associated with their regimen, and the benefits of making a change. Dose reduction should be considered if clinically appropriate.

2. Using monotherapy is recommended whenever possible. Monotherapy reduces the total dose exposure for consumers of medication that affect the brain.

3. Collaborative development of strategies for adherence with clients will maximize clinical benefit and avoid dose increases.

4. Prescribers should ensure that the dose and duration of medication trials are adequate and consistent with evidence-based guidelines. Medication should be given an adequate time to work prior to increasing the dose.

5. Careful diagnostic evaluation over time and consideration of character structure will assist in avoidance of medication treatment and escalating doses for clients whose symptoms will respond better to psychosocial treatments.

6. 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 high dosing.

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. 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 helpful to consumers and promote dialogue with prescribers.

9. Gradual medication tapers are recommended when reducing doses. 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.

10. Strategies for **communication by prescribers with the consumer’s primary care provider** will be helpful in addressing medical causes of psychiatric symptoms which otherwise may result in high doses or polypharmacy.

11. **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.

12. For consumers receiving high doses of psychotropics, **periodic efforts should be made to taper the dose** once the consumer is doing well.

### Annotated Bibliography for Reducing Higher than Recommended Doses of Psychotropic Medications

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](http://www.psyckes.org) provide more in-depth information and a critical review of important scientific articles.

[Note: There is very little scientific literature on the use of higher than recommended doses of psychotropic medications in children and adolescents.]

1. **Baldessarini RJ, Cohen BM, Teicher MH. Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses.** *Archives of General Psychiatry 1988* vol 45, pp79-91

   This classic review paper from the pre-second generation antipsychotic (SGA) era describes the gap between scientific research and application to clinical practice. The paper reviews dose-response and blood level-response studies in first-generation antipsychotics over 2 decades. These findings have been replicated in studies involving second-generation antipsychotics, with dose-response curves for all SGAs peaking at moderate doses.

   - In acute psychosis moderate doses of antipsychotics (600 mg of chlorpromazine equivalents) were as effective as higher doses for symptom reduction, time to response, and length of inpatient stay. Doses below 300mg chlorpromazine equivalents were more effective than placebo, but less effective than higher doses.
   - There is no scientific evidence from RCTs that rapid neuroleptization improves clinical outcome.
   - A combined study analysis of long-term treatment data also demonstrated optimal response at moderate doses of medication, with reduced duration of response at low and high doses.

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 Neuropsychopharmacology and Biological Psychiatry 2006* vol 30, p1009-1014

   This study was completed in Japan with 17 patients with schizophrenia on 2 first-generation antipsychotics (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.


Antidepressant doses approved by the FDA include a wide dose range for most antipsychotics, with conflicting evidence on how much is enough. This meta-analysis of 74 articles analyzes the relationship between antidepressant dose and response in outpatient studies. The analysis stratified doses in two ways: low and high, and low, medium and high. For fluoxetine the doses were ≤45 mg and >45 mg for the two tier analysis, and <27.5 mg, 27.5-62.5 mg, and >62.5 mg for the three tiered analysis. All antidepressants were similarly stratified by dose.

- The medium dose level had a weighted mean difference in HAM-D scores of 1.6 points lower when compared to the low dose. The high dose level was 2.3 points lower in mean Ham-D scores when compared to the low dose.
- The small reduction in Ham-D scores at the medium and higher dose levels is too small to be clinically apparent.


The CATIE trial in adults allowed olanzapine (Zyprexa) doses up to 30 mg, higher than the recommended maximum in PORT guidelines. Some clinicians have felt that the results of the CATIE trial which favored olanzapine may be attributed to this dosing. Case reports of high doses of olanzapine in youth have been associated with improved response and lack of adverse effects. This clinical trial studied 18 children 10-18 years old with schizophrenia who had been resistant or intolerant to at least 2 antipsychotic medications. The youth were randomized in double blind fashion to either olanzapine or clozapine (Clozaril) groups. Each medication was flexibly dosed to a maximum of 30 mg of olanzapine or 900 mg of clozapine. Response criteria were a 30% reduction in the total BPRS score as well as a CGI of “1” (very much improved) or “2” (much improved). The results, though the n is small, suggest that moving to clozapine is more effective than using high dose olanzapine in this population and does not cause more serious metabolic effects.

- Mean olanzapine (Zyprexa) dose was 26 mg in youth who completed the study. Mean clozapine (Clozaril) dose was 478 mg.
- Response rate to clozapine was 66%; response rate to “high dose” olanzapine was 33%.
- There were no differences between the two drugs in metabolic or other side effects.
- 70% of the high dose olanzapine non-responders subsequently responded to clozapine.


References

