High-Dose Therapy in Treatment-Refractory Psychosis: A Retrospective Study

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ABSTRACT

Objective: To examine the impact of antipsychotic dose adjustments (mainly reduction) on the efficacy and tolerability of antipsychotic medications (APMs) to facilitate hospital discharge in long-term hospitalized forensic patients with treatment-refractory psychosis.

Methods: This was a retrospective review of the medical charts of 22 patients with psychosis who were discharged from January 2020 to August 2020 from a long-term state psychiatric facility after restoration of their competency to stand trial. Due to the lack of specific guidelines, the high-dose therapy was defined as a dose ≥ 50% above the average package insert dose. The primary outcome was discharge time after the antipsychotic dosing adjustments.

Results: Sixty-eight percent of subjects, who were hospitalized for a mean ± SD total of 11.6 ± 5.3 months, were discharged after 2.3 ± 0.78 months of 44.4% antipsychotic dose reduction. Two patients, who were hospitalized for 14.5 ± 6.7 months, were discharged after 4 months of optimizing their subtherapeutic doses. Five patients, who were already receiving effective dosages, were discharged after a total hospital duration of 6.8 ± 2.17 months.

Conclusions: The results from this study extend the finding of beneficial effects of antipsychotic dose reduction from prior reports to the forensic population.

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High-dose antipsychotic medications (APMs) and polypharmacy (mega polypharmacy) frequently occur, particularly in the treatment-refractory schizophrenia population. Despite the lack of managed care pressures to quickly discharge patients from long-term state psychiatric hospitals, antipsychotic doses rapidly escalate beyond the conventional dosing range without waiting for the delayed antipsychotic response. This rapid dose escalation deprives patients of the chance to respond to the lowest effective dose, which is generally the most tolerable. Often, higher antipsychotic doses are justifiably used to manage behavioral aggression observed during acute psychosis rather than to prevent relapse (ie, maintenance doses) or treat early psychosis.[1] However, the concern is not the high antipsychotic doses used during acute psychosis, but the repeated dose escalations after each behavioral disruption, often with no poststabilization dose adjustments. Although some suggest that the continuation of high-dose therapy effectively prevents relapse,[2] there is no formal evidence to support this point of view, except data from a few case reports and case series, which need to be interpreted cautiously due to publication bias. In contrast, the evidence against high-dose therapy started decades ago[3] and has only grown with time.[4–11]

Lack of evidence-based guidelines for effective maintenance doses as opposed to dosing recommendations for acute psychosis[12,13] may be one reason for the continuation of high-dose therapy, especially in the treatment-refractory population. An initial nonresponse and urgency to treat also encourage high-dose treatment, creating a potential bias in perception of outcome. Some patients may also exaggerate or falsely report improvement to please their providers. Opposing guidelines have added further complexity with regard to defining effective maintenance doses. For example, the American Psychiatric Association guidelines recommend using the lowest effective doses for maintenance treatment.[14]

In contrast, the Expert Consensus Guidelines suggest continued use of antipsychotic doses effective during acute psychosis.[2] It is worth noting that even the US Food and Drug Administration (FDA)–approved dosages, determined in a near-perfect patient population in preclinical trials, may not be helpful in real-world patients who often have comorbidities. The postmarketing deviations from FDA-approved dosages can often be explained based on genetically mediated interindividual variability in plasma levels or drug interactions.[15] In addition, excessive sedation with high-dose therapy may also be misperceived as an improvement in psychosis. However, the high-dose therapy may also result in some not so benign adverse effects, ranging from extrapyramidal symptoms (EPS)[16] to potentially fatal cardiac arrhythmias[17] and neuroleptic malignant syndrome.[18]

Clinical Points

- There is growing evidence against high-dose therapy in patients with psychosis.
- Beneficial effects of antipsychotic dose reduction may be extended to the forensic population.
- Clinicians should cautiously consider antipsychotic dose reduction to facilitate hospital discharge in the long-term hospitalized forensic population.

In contrast, lower doses have been associated with significantly lower risk for some of these adverse effects.[6,19–21] In addition, high-dose therapy with APMs with anticholinergic properties are associated with dryness of the mouth (resulting in partial or complete loss of taste), retention of urine, blurring of vision, constipation, loss of sweating, tachycardia, and a further worsening of preexisting cognitive dysfunction. Many APMs can also cause postural hypotension and dose-dependent weight gain, increasing the risk for metabolic syndrome in a patient population with a significant preexisting risk for medical comorbidities, most notably diabetes and hypertension.[22]

Mechanistically, continued high-dose therapy exposes patients to higher dopamine-2 (D_2) receptor blockade than that required to control psychosis (ie, 60%–80%).[23–25] Any D_2 receptor blockade ≥ 80% is associated with adverse effects, especially EPS and hyperprolactinemia. High antipsychotic doses also promote medication nonadherence due to adverse effects, which makes it difficult to maintain stability after hospital discharge and to reintegrate these patients into the community, resulting in so-called "revolving door syndrome," wherein patients are admitted repeatedly with significant health costs. A retrospective review[26] showed that high-dose antipsychotic treatment to manage psychosis at hospital discharge might increase the risk for readmission in patients with borderline personality disorder. Another study[27] reported an increased readmission rate within 6 months of hospital discharge for patients on antipsychotic polypharmacy.

These are reasons to prioritize an adequate trial with conventional antipsychotic doses, which can be facilitated by monitoring EPS or plasma drug and prolactin levels. Although prior studies have documented the positive effects of dose reduction in schizophrenia patients, there is little evidence to support lower doses in the forensic population residing in long-term psychiatric facilities. This retrospective study demonstrates how informed dosing adjustments can enhance antipsychotic effectiveness to facilitate competency restoration and hospital discharge of forensic subjects from a long-term state psychiatric facility.

METHODS

A review was conducted of medical charts of 22 inpatients at or after their discharge (January 2020 to August 2020) from a long-term state psychiatric hospital back to the court system to stand trial. This was a retrospective review of the medical charts of discharged patients, which makes it difficult to obtain informed consents from the study subjects. In addition, these patients were in the hospital for restoration of competency, reducing the validity of informed consents. Since the findings from this study are of high clinical relevance in an understudied population, it was important to communicate the study results to the clinicians working in a forensic inpatient setting. Every effort was made to keep the personal health information of these patients confidential.

Study Subjects

All patients selected for this study were males who responded to their antipsychotic treatment, facilitating competency restoration to stand trial as determined by the state hospital's forensic staff. The study subjects were managed in a single inpatient unit and were discharged back to the state court system to stand trial by a staff psychiatrist during 7 months of inpatient management. The psychiatric diagnoses of these patients were established by a live interview with the treatment team and review of the medical records by certified psychiatrists after the hospital admission using *DSM-5* criteria. However, regardless of their diagnosis, all patients were treated with 1 or more APMs for their psychosis as the primary presenting symptom. The antipsychotic-induced adverse effects were physically monitored for extrapyramidal symptoms, and drug and prolactin levels were monitored where indicated and consented by the patients. The patients' demographic data, diagnoses, APM(s), change in doses, hospital duration, and time to discharge after dose adjustments are presented in Table 1.

Study Data and Procedures

All study data were derived from the discharged patients' electronic medical records by the author to examine the quality of clinical documentation. The missing data are reported in Table 1. The primary outcome assessed was the time to discharge after dose adjustments to the antipsychotic medications. Since there are no clear guidelines to differentiate between conventional and high antipsychotic doses and to account for high variability in dose equivalency to occupy 60% to 80% D_2 receptor blockade, the high-dose therapy was defined as a dose ≥ 50% above average package insert dose. Any dose roughly ≥ 50% of the maximum package insert dose was labeled as a high-dose therapy. A subtherapeutic dose was defined as less than the lowest effective dose in the package insert, except for risperidone due to postmarketing effectiveness of lower doses. High antipsychotic dosages were not adjusted if the plasma levels were within the laboratory reference range. The doses of 4 patients who were on long-acting injectables (LAIs) were also adjusted based on their oral dose equivalency and prolactin and antipsychotic plasma levels. Clinically, effective dose was described as the dose that produced an antipsychotic response (≥ 20% decrease in total Positive and

Table 1. Demographic and Admission and Discharge Data for the Patients

Patients	Antipsychotic Medication 1 (APM-1)				Antipsychotic Medication 2 (APM-2)				Concomitant Medications	Hospital Duration (months)	Postdose Adjustment Changes in Response and Adverse Effects	Time to Discharge After APM Dose Change
	APM-1 Admission Dose	Drug and Prolactin Levels (ng/mL)	APM-1 Discharge Dose	Plasma and Prolactin Levels (ng/mL)	APM-2 Admission Dose	Drug and Prolactin Levels (ng/mL)	APM-2 Discharge Dose	Plasma and Prolactin Levels (ng/mL)				
Patient 1: age 40 y, Asian Diagnosis: amphetamine use disorder in early sustained remission	Olanzapine 50 mg/d	Drug: NA Prolactin: NA	Olanzapine 20 mg/d	Plasma: NA Prolactin: NA	Risperidone 1 mg/d	Drug: NA Prolactin: NA	Risperidone gradually discontinued	Plasma: NA Prolactin: NA	None	9.5	Less negative symptoms; improved cognition with conceptual flexibility; improved hygiene and cognition; brighter affect; decreased pseudoparkinsonion symptoms	4 months
Patient 2: age 41 y, Black Diagnosis: schizophrenia	Risperidone 6 mg/d	Drug: NA Prolactin: 36.9	Risperidone 3 mg/d	Plasma: NA Prolactin: NA	Loxapine 100 mg/d	Drug: NA Prolactin: NA	Loxapine 100 mg/d	Plasma: NA Prolactin: NA	Metoprolol 50 mg twice/d; docusate sodium 250 mg at bedtime; chlorthalidone 25 mg in the morning for hypertension	10	Improved psychosis; improved attention and concentration; reduced tremors, sedation, muscle stiffness; increased social activities; more spontaneous in responses	2 months
Patient 3: age 30 y, Black Diagnosis: schizophrenia, malingering	Clozapine 550 mg/d	Drug: clozapine = 321 norclozapine = 133 Prolactin: NA	Clozapine 600 mg/d	Plasma: clozapine = 575 norclozapine = 220 Prolactin: NA	…	…	…	…	Olanzapine 5 mg PRN for agitation; docusate sodium 250 mg twice/d for constipation; bisacodyl 10 mg/d PRN; magesium citrate 1 bottle every 3 d PRN; acetaminophen 650 mg every 6 hours PRN for pain	19	Slight improvement in social activities; brighter affect; no change in adverse effects	4 months
Patient 4: age 30 y, White Diagnosis: major depressive disorder, recurrent, severe, with psychosis; alcohol use disorder in early sustained remission	Olanzapine 10 mg /d	Drug: NA Prolactin: NA	Olanzapine 30 mg/d	Plasma: NA Prolactin: NA	…	…	…	…	Mirtazapine 30 mg oral at bedtime; escitalopram 20 mg oral at bedtime; docusate sodium 250 mg oral 2 times/d; omega 3 fatty acids 1 capsule oral 2 times/d	10	Significantly less depression and comorbid obsessive-compulsive symptoms; no change in adverse effects	4 months

(continued)

Table 1 (continued).

Patients	Antipsychotic Medication 1 (APM-1)				Antipsychotic Medication 2 (APM-2)				Concomitant Medications	Hospital Duration (months)	Postdose Adjustment Changes in Response and Adverse Effects	Time to Discharge After APM Dose Change
	APM-1 Admission Dose	Drug and Prolactin Levels (ng/mL)	APM-1 Discharge Dose	Plasma and Prolactin Levels (ng/mL)	APM-2 Admission Dose	Drug and Prolactin Levels (ng/mL)	APM-2 Discharge Dose	Plasma and Prolactin Levels (ng/mL)				
Patient 5: age 35 y, White Diagnosis: unspecified schizophrenia	Olanzapine 60 mg oral at bedtime	Drug: 257 Prolactin: patient refused	Olanzapine 30 mg oral at bedtime	Plasma: patient refused Prolactin: patient refused	Fluphenazine 15 mg 2 times/d	Drug: NA Prolactin: patient refused	Gradually discontinued in 6 wk	Plasma: NA Prolactin: NA	Diphenhydramine 50 mg every 12 hours PRN for EPS; fluphenazine 10 mg every 12 hours PRN for agitation; zolpidem 5 mg at bedtime PRN for insomnia	18	Improved psychosis; improved attention and concentration; no dryness of mouth; less dizziness; less confusion	0.75 months
Patient 6: age 29 y, White Diagnosis: unspecified schizophrenia; alcohol use disorder in early sustained remission	Olanzapine 30 mg oral 2 times/d	Drug: NA Prolactin: NA	Olanzapine 20 mg oral 2 times/d	Plasma: NA Prolactin: NA	…	…	…	…	Divalproex sodium 1,000 mg oral 2 times/d; methotrexate 15 mg/wk for arthritis	10	Improved psychosis; reduced sedation; less dryness of mouth; improved social activities; improved memory; brighter affect	2 months
Patient 7: age 24 y, Black Diagnosis: schizophrenia	Olanzapine 40 mg oral at bedtime	Drug: 109 Prolactin: 108	Olanzapine 20 mg oral at bedtime	Plasma: NA Prolactin: NA	Risperidone 7 mg/d oral	Drug: risperidone/paliperidone lithium = 17.3/48.1 Prolactin: 108	Risperidone 4 mg/d oral	Plasma: NA Prolactin: NA	Divalproex sodium 500 mg oral at bedtime	6	Reduced psychosis; no suicidality; improved sleep and appetite; improved short-term memory; improved psychosis	2 months
Patient 8: age 33 y, Hispanic Diagnosis: bipolar I disorder; amphetamine, alcohol, and cannabis use disorders, all in early sustained remission	Risperidone 4 mg/d oral	Drug: NA Prolactin: 42.2	Risperidone 1.5 mg/d oral	Plasma: NA Prolactin: NA	…	…	…	…	Trazodone 100 mg oral at bedtime; levothyroxine 50 mcg oral every morning; lithium 450 mg oral 2 times/d	6	Reduced behavioral disruption; reduced psychosis; less stiffness and rigidity; less dizziness; brighter affect	2 months
Patient 9: age 35 y, Black Diagnosis: schizophrenia	Olanzapine 30 mg/d	Drug: NA Prolactin: NA	Olanzapine 30 mg/d	Plasma: NA Prolactin: NA	…	…	…	…	Diphenhydramine 50 mg oral at bedtime	5	No medication changes, took time to stabilize and become competent for discharge	…
Patient 10: age 38 y, White Diagnosis: unspecified schizophrenia; amphetamine use disorder in early sustained remission	Olanzapine 65 mg oral at bedtime	Drug: NA Prolactin: NA	Olanzapine 60 mg oral at bedtime	Plasma: NA Prolactin: NA	…	…	…	…	Melatonin 5 mg oral PRN for insomnia; fluphenazine 5 mg oral PRN every 8 hours; docusate sodium 250 mg oral 2 times/d; omeprazole 20 mg oral every morning	8	Longer time to respond; improved psychosis; no major change in adverse effects; reduced need for PRN fluphenazine	2 months

(continued)

Table 1 (continued).

Patients	Antipsychotic Medication 1 (APM-1)				Antipsychotic Medication 2 (APM-2)				Concomitant Medications	Hospital Duration (months)	Postdose Adjustment Changes in Response and Adverse Effects	Time to Discharge After APM Dose Change
	APM-1 Admission Dose	Drug and Prolactin Levels (ng/mL)	APM-1 Discharge Dose	Plasma and Prolactin Levels (ng/mL)	APM-2 Admission Dose	Drug and Prolactin Levels (ng/mL)	APM-2 Discharge Dose	Plasma and Prolactin Levels (ng/mL)				
Patient 11: age 42 y, Hispanic Diagnosis: schizoaffective disorder, bipolar	Fluphenazine decanoate 100 mg IM every Friday	Drug: 5.1 (reference range, 1–10) Prolactin: NA	Fluphenazine decanoate 100 mg IM every other Friday	Plasma: NA Prolactin: NA	Ziprasidone 80 mg oral 2 times/d with meals	Drug: NA Prolactin: NA	Ziprasidone 80 mg oral 2 times/d with meals	Plasma: NA Prolactin: NA	Levomefolate 15 mg oral every morning	10	Reduced tremors; less muscle stiffness; less sedation; brighter affect; more responsive with better attention and concentration; increase in social activities	2 months
Patient 12: age 39 y, White Diagnosis: unspecified schizophrenia; cannabis and alcohol use disorders, both in early sustained remission; epilepsy, unspecified	Olanzapine 50 mg oral at bedtime	Drug: 227 Prolactin: NA	Olanzapine 20 mg oral at bedtime	Plasma: 108 Prolactin: NA	…	…	…	…	Mirtazapine 45 mg oral at bedtime; levetiracetam 1,000 mg oral twice/d; trazodone 50 mg oral at bedtime; omeprazole 20 mg oral at bedtime	24	Less sedation; less dryness of mouth; less constipation; tachycardia improved; no significant change in psychosis	3 months
Patient 13: age 34 y, White Diagnosis: schizophrenia	Paliperidone palmitate 117 mg IM once/month	Drug: NA Prolactin: NA	Paliperidone palmitate 117 mg IM once/month	Plasma: NA Prolactin: NA	…	…	…	…	Omega 3 fatty acids 2 capsules 2 times/d	8	No change in adverse effects; psychosis improved with time with no dose change in the long-acting injectable	…
Patient 14: age 39 y, Hispanic Diagnosis: unspecified schizophrenia	Haloperidol decanoate IM 200 mg every other Friday	Drug: 25 Prolactin: 52.9	Haloperidol decanoate IM 150 mg every other Friday	Plasma: NA Prolactin: NA	Olanzapine 40 mg/d	Drug: 247 Prolactin: 52.9	Olanzapine gradually discontinued	Plasma: NA Prolactin: NA	Divalproex sodium extended release 500 mg oral at bedtime	11	Improved attention; less responsive to internal stimuli; less sedated; less dryness of mouth; brighter affect; better hygiene; less drooling	3 months
Patient 15: age 39 y, Asian Diagnosis: schizophrenia; amphetamine, alcohol, and cannabis use disorders, all in early sustained remission	Haloperidol decanoate IM 200 mg every 4th Friday	Drug: NA Prolactin: NA	Haloperidol decanoate IM 200 mg every 4th Friday	Plasma: NA Prolactin: NA	Olanzapine 10 mg oral at bedtime	Drug: NA Prolactin: NA	Olanzapine 10 mg oral at bedtime	Plasma: NA Prolactin: NA	Mirtazapine 15 mg oral at bedtime	6	No dose changes were made, patient gradually became competent; no adverse effects recorded	…

(continued)

Table 1 (continued).

Patients	Antipsychotic Medication 1 (APM-1)				Antipsychotic Medication 2 (APM-2)				Concomitant Medications	Hospital Duration (months)	Postdose Adjustment Changes in Response and Adverse Effects	Time to Discharge After APM Dose Change
	APM-1 Admission Dose	Drug and Prolactin Levels (ng/mL)	APM-1 Discharge Dose	Plasma and Prolactin Levels (ng/mL)	APM-2 Admission Dose	Drug and Prolactin Levels (ng/mL)	APM-2 Discharge Dose	Plasma and Prolactin Levels (ng/mL)				
Patient 16: age 27 y, White Diagnosis: schizophrenia; cocaine, opioid, and alcohol use disorders, all in early sustained remission	Ziprasidone 120 mg oral twice/d	Drug: NA Prolactin: NA	Ziprasidone 120 mg oral 2 times/d	Plasma: NA Prolactin: NA	…	…	…	…	Buspirone 20 mg oral 2 times/d; lithium 600 mg/d; melatonin 5 mg oral at bedtime	5	No dosing changes, except lithium reduced; less sedation; more socially active; less tremors	NA
Patient 17: age 36 y, White Diagnosis: unspecified schizophrenia; alcohol use disorder in early sustained remission	Olanzapine 40 mg oral at bedtime	Drug: NA Prolactin: NA	Olanzapine 20 mg oral at bedtime	Plasma: NA Prolactin: NA	…	…	…	…	Olanzapine 10 mg oral PRN	9	Improved psychosis; less sedation; more active; less dryness of mouth; less constipation and reduced use of PRN laxative	2 months
Patient 18: age 28 y, Hispanic Diagnosis: unspecified schizophrenia; amphetamine and cocaine use disorder in early sustained remission	Olanzapine 40 mg oral at bedtime	Drug: NA Prolactin: NA	Olanzapine 40 mg oral at bedtime	Plasma: NA Prolactin: NA	…	…	…	…	Divalproex sodium 500 mg oral every morning and 1,000 mg oral at bedtime; citalopram 40 mg oral every morning	10	No dose change; citalopram optimized; more socially active; slow reduction in psychosis	NA
Patient 19: age 29 y, Hispanic Diagnosis: unspecified schizophrenia	Olanzapine 60 mg/d	Drug: NA Prolactin: 79	Olanzapine 40 mg/d	Plasma: NA Prolactin: NA	Risperidone 6 mg/d	Drug: NA Prolactin: 79	Risperidone gradually discontinued	Plasma: 66.5 (on 2 mg of risperidone) Prolactin: NA	Sertraline 200 mg/d oral; hydroxyzine 25 mg oral at bedtime	10	Improved social activities; improved psychosis; better sleep; decreased sedation, tremors, and dryness of mouth	1.5 months
Patient 20: age 32 y, Asian Diagnosis: malingering; schizophrenia by history	Olanzapine 60 mg/d	Drug: 86.8 Prolactin: 50	Olanzapine 20 mg/d	Plasma: NA Prolactin: NA	Haloperidol 25 mg/d	Drug: 39 Prolactin: 50	Haloperidol 25 mg/d	Plasma: 17 Prolactin: NA	Discontinued third antipsychotic, fluphenazine 5 mg/d	21	Brighter affect; less muscle stiffness; less pseudoparkinsonion symptoms; less fatigue; more socially active	3 months
Patient 21: age 26 y, Black Diagnosis: opioid use disorder in early remission; antisocial personality disorder	Olanzapine 30 mg/d	Drug: NA Prolactin: NA	Olanzapine discontinued	…	…	…	…	…	Mirtazapine 30 mg oral at bedtime; diphenhydramine 50 mg oral 2 times/d	8.5	Complete recovery from psychosis despite stopping olanzapine; all adverse effects disappeared	2 months

(continued)

Table 1 (continued).

Patients	Antipsychotic Medication 1 (APM-1)				Antipsychotic Medication 2 (APM-2)				Concomitant Medications	Hospital Duration (months)	Postdose Adjustment Changes in Response and Adverse Effects	Time to Discharge After APM Dose Change
	APM-1 Admission Dose	Drug and Prolactin Levels (ng/mL)	APM-1 Discharge Dose	Plasma and Prolactin Levels (ng/mL)	APM-2 Admission Dose	Drug and Prolactin Levels (ng/mL)	APM-2 Discharge Dose	Plasma and Prolactin Levels (ng/mL)				
Patient 22: age 43 y, Hispanic Diagnosis: schizoaffective disorder, bipolar type	Olanzapine 40 mg/d	Drug: 60 Prolactin: NA	Olanzapine 20 mg oral at bedtime	Plasma: NA Prolactin: NA	…	…	…	…	Sitgliptin 100 mg oral every morning; metformin 1,000 mg oral 2 times/d	13	Increased cooperativeness; more physically active; pleasant interactions with staff and peers; no active psychosis; improved affective symptoms; improved sleep and appetite	3 months

Abbreviations: IM = intramuscular, NA = not available, PRN = as needed.
Symbol: … not applicable.

Negative Syndrome Scale[28] scores) without significant adverse effects, such as EPS and hyperprolactinemia.

RESULTS

As shown in Table 1, all 22 patients were adult males with a mean ± SD age of 34.04 ± 5.49 years. Eight patients were White, 6 were Hispanic, 5 were Black, and 3 were Asian. Unspecified schizophrenia was the primary diagnosis in 8 patients, schizophrenia in 7, and schizoaffective disorder, bipolar type in 2. One patient had a primary diagnosis of major depressive disorder with psychosis and another of bipolar affective disorder with psychosis. Although only 2 patients had a primary diagnosis of amphetamine and opioid use disorder, substance use disorder was the most common comorbid diagnosis in these cases, including amphetamine use disorder in 4 patients, alcohol use in 7, cannabis in 3, cocaine in 2, and opioid use in 2. Malingering was a primary diagnosis in one and a comorbid diagnosis in another reviewed case. One of the cases also had a comorbid diagnosis of antisocial personality disorder.

A total of 22 patients, hospitalized for a mean ± SD of 10.77 ± 5.08 months, were discharged from a state psychiatric facility managed by a single staff psychiatrist over 7 months. Seventeen (77%) of 22 patients, hospitalized for 11.94 ± 5.3 months, were discharged after 2.5 ± 0.93 months of dose adjustments or reduced polypharmacy. Fifteen (68%) of these patients, hospitalized for a total of 11.6 ± 5.3 months, were discharged after 2.3 ± 0.78 months of their dose reduction or reduced polypharmacy. Two patients, hospitalized for 14.5 ± 6.7 months, were discharged after 4 months of optimizing their subtherapeutic dosages (Table 1). No dose adjustments were made for the rest of the patients (23%), as they were already taking effective doses and were discharged after being hospitalized for 6.8 ± 2.17 months. The 15 patients in the dose reduction group had an average of 44.4% reduction in their first APM. Nine of these patients had antipsychotic polypharmacy, of which 4 had their second APM discontinued, and one had dose reductions in both the first and second APM (Table 1). Only 4 of 22 patients were on LAIs. Olanzapine was the most frequently prescribed orally administered high-dose APM in this group (ie, 12 of 18 patients). Still, 1 of these patients had a subtherapeutic dose, and 2 did not need any dosing changes, thus leaving 9 patients with a mean dose of 51.7 mg/d reduced to 27.8 mg/d. In contrast, risperidone was reduced by ≥ 50% (10 mg/d to 4.5 mg/d) in 2 patients.

DISCUSSION

This is the first retrospective study in forensic patients hospitalized in a long-term psychiatric facility, to my knowledge, to report the positive effects of antipsychotic dose reduction on treatment effectiveness, competency restoration, and hospital discharge with no symptom relapse. The utility of dose adjustments is supported by a longer average hospital stay in patients before dose reduction (9.3 months) compared to after dose reduction (2.3 months). However, the shortest hospitalization was reported in 2 patients who were already on effective doses (ie, < 7 months), and the longest hospital duration was observed in patients who required optimization of their subtherapeutic doses (ie, 14.5 months). These results suggest that response to increasing a subtherapeutic dose takes longer than a dose reduction. This could be attributable to a decrease in adverse effects that precedes loss of, or decrease in, efficacy following a dose reduction. However, relapse after discharge cannot be completely ruled out, despite continued stability for a 10-week hospitalization after a slow and gradual dose reduction being associated with a relatively low risk for relapse.[10,11]

Of note, a total hospitalization of > 11 months in this study is longer than the 6 months required to restore competency in 75% of a similar patient population in earlier studies.[29,30] Interestingly the average dose reduction of 44.4% in this study is close to a 42% dose reduction in a randomized, rater-blinded trial with no relapse.[10] Similarly, 50% dose reduction in 2 randomized controlled trials was not associated with any worsening in psychosis but instead resulted in an improvement in negative and cognitive symptoms.[31,32] These findings are further supported by a significant functional improvement in > 50% of the study subjects after about 60% reduction in the antipsychotic dose in another study.[11] Along the same lines, a comprehensive Cochrane review[4] found no clear advantages of increasing the dose over continuing the previous dose.

Although high-dose therapy is justifiable to manage acute psychosis and associated behaviors, the high doses are often continued as maintenance doses beyond patients' stabilization. The rationale provided is the biological differences between treatment-refractory patients and the general patient population, justifying the continuation of high-dose therapy to avoid aggression and violence. However, one can also make a counterargument against high-dose therapy, as it carries an increased risk for adverse effects in biologically vulnerable patients with a high prevalence of medical, substance use, and psychiatric comorbidities. More importantly, there are no formal data to support high-dose therapy except for a few case reports and case series, which may overrepresent the evidence due to publication bias. There is only 1 study[33] with an LAI that used high enough doses to be relevant to this discussion. Although there were no significant differences in efficacy between the top 3 LAI doses, the adverse effects were numerically higher with the highest dose of 200 mg/month than with the lower dosages. In contrast, data from most studies[18,33–38] with l LAI reported effective maintenance dosages that are more like conventional than high dosages.

Executive cognition is one of the critical elements required for competency restoration. Since dopamine is one of the most important neurotransmitters for executive cognitive function,[39] the continuation of high-dose therapy with excessive dopamine blockade can further compromise preexisting executive dysfunction, delaying competency restoration. This view is supported by improved performance on several cognitive measures without relapse after reduction in maintenance doses or even complete discontinuation of APMs.[32,40] In another study,[41] patients found to have a short-term increase in relapse rates after the dose reduction were reported to have a higher rate of symptomatic and functional remission than those who were continued on their previous doses over a 7-year follow-up.[42] In addition, improved performance was reported on measures of psychosocial adjustment in patients receiving the low dose compared to those receiving standard doses.[43] Moreover, even discontinuation of APMs was associated with more extended recovery periods, with no relapse in up to one-third of the schizophrenia patients who stopped taking their APM.[44] For these reasons, the goal of antipsychotic dose adjustments in this study was to achieve an effective dose, defined as providing the best compromise between efficacy and tolerability, and allowing enough dopamine function for the forensic rehabilitation to succeed.

However, extreme caution is required to discontinue an APM or to lower its dose below the standard doses due to increased risk for relapse[43] until biomarkers are developed to identify patients who will do well on reduced doses or even after discontinued medication(s).[32,40,44] Until then, high-dose therapy should only be employed after ruling out the confounding effects of environmental stress, pharmacogenetic variance, seasonal changes in symptoms, or medication nonadherence on patients' psychopathology. Also, a physical examination for EPS and laboratory investigations for prolactin and drug levels can help determine effective dosages. Uninformed antipsychotic polypharmacy can be wholly ineffective or intolerable and should be avoided or replaced by logical antipsychotic combinations. In this study, 4 patients in the dose reduction group were successfully stabilized by reducing their first APM dose and discontinuing their second APM. However, the key to a successful dose reduction/discontinuation is to avoid abrupt stoppage and follow a gradual dose reduction while monitoring psychotic relapse and discontinuation symptoms, such as rebound psychosis and akathisia.[8]

Still, there will be a minority of patients that will require and respond to high-dose therapy with no plausible genetic or clinical explanations for it. However, high-dose treatment should only be employed after failing an adequate trial with the conventional doses of APMs. Finally, LAIs are more effective in preventing relapse than oral APMs due to improved medication adherence, and LAIs should be a priority, especially in patients with a known history of medication nonadherence.

Limitations

The findings of this study should be interpreted with caution, as they are based on retrospective chart review without a priori hypotheses. Another limitation is the naturalistic setting of the study data, which limits providing control for various confounding factors that may affect the study results. In addition, lack of clear definition of effective maintenance doses makes it difficult to define various dosing levels and accurately interpret findings.

CONCLUSION

This study is the first to extend findings from earlier studies to a forensic population showing the effectiveness of antipsychotic dose reduction in facilitating competency restoration, hospital discharge, and community reintegration in a long-term hospitalized forensic patient population. The reduced dosages also offered a significantly better adverse effect profile, which is of high clinical significance in a patient population with multiple preexisting cognitive deficits and a high prevalence of medical, substance use, and psychiatric comorbidities.

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