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# Subjective Medication Satisfaction With Antipsychotic Polypharmacy in a Naturalistic Inpatient and Outpatient Sample

Martijn J. Kikkert, PhD<sup>a,\*</sup>; Liselotte de Mooij, MSc<sup>a</sup>; Mariken de Koning, MD, PhD<sup>a</sup>; and Jack Dekker, PhD, Prof<sup>a,b</sup>

## ABSTRACT

**Objective:** The aim of this study was to examine satisfaction with pharmacologic treatment in patients who received antipsychotic polypharmacy compared to antipsychotic monotherapy.

**Methods:** This longitudinal cohort study was conducted in two mental health care institutes in Amsterdam, the Netherlands, among a randomly selected sample of in- and outpatients with a severe mental illness. Analyses were performed on data collected in 2011 for 185 patients who were diagnosed with schizophrenia or unspecified psychosis according to *DSM-IV* criteria. The outcome measure was the Treatment Satisfaction Questionnaire for Medication, version II. One-way analyses of covariance were performed to examine differences in treatment satisfaction between patients who received antipsychotic polypharmacy compared to antipsychotic monotherapy while controlling for the effects of clozapine, antipsychotic dose, and use of long-acting injectable antipsychotics.

**Results:** Twenty percent of patients in this sample received 2 antipsychotic agents; in half of those patients, this involved a combination with clozapine. Polypharmacy resulted in less satisfaction with side effects compared to monotherapy ( $P = .002$ ). No difference was found in perceived effectiveness ( $P = .168$ ) or overall medication satisfaction ( $P = .379$ ).

**Conclusions:** These results confirm that antipsychotic polypharmacy is common in a random in- and outpatient sample. Patients who receive 2 antipsychotic agents are just as positive about the effectiveness and ease of use of and overall satisfaction with their medication compared to those who receive antipsychotic monotherapy. They are, however, less satisfied with perceived side effects of their medication, which may indicate that side effect profiles of antipsychotic combinations are less favorable.

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<sup>a</sup>Arkin, Mental Health Care Institute Amsterdam, Amsterdam, the Netherlands

<sup>b</sup>Vrije Universiteit, Faculty of Behavioural and Movement Sciences, Clinical Psychology, Amsterdam, the Netherlands

\*Corresponding author: Dr M. Kikkert, PhD, Arkin, Klaprozenweg 111, 1033NN Amsterdam, the Netherlands (martijn.kikkert@arkin.nl).

One of the interventions in the treatment of patients with a psychotic disorder is the use of antipsychotic medication. Unfortunately, approximately a third of patients do not respond sufficiently to antipsychotic medication.<sup>1</sup> In those cases, clinicians can alter the dose, switch to another agent, or, if a patient has not responded to 2 different antipsychotics, each with adequate dose and duration and with ensured adherence, switch to clozapine. Another option is to combine 2 antipsychotic agents. Combining more than 1 antipsychotic medication is referred to as antipsychotic polypharmacy (APP). This is sometimes done if a patient does not respond well to clozapine or if clozapine is not an option for any reason. APP can also be used to reduce specific side effects or positive or negative symptoms.<sup>2</sup>

Treatment guidelines do not recommend APP as there is an insufficient evidence base to support it.<sup>3,4</sup> There is, however, a distinct discrepancy between these guidelines and clinical practice. Studies show that APP is utilized in approximately 10%–30% of patients with a psychotic disorder<sup>5–7</sup> and remains a common practice in all parts of the world.<sup>8</sup>

Although there are some studies to which clinicians can refer, information concerning which combinations are more likely to give the best outcome and when to use them is very limited. This may not be a bad thing, but it does mean that the quality of the pharmacologic treatment depends more heavily on the experience and skills of the clinician and on trial-and-error experiments. As such, APP may result more often in suboptimal or poor medical treatment.

Obviously, in treatment-resistant patients, looking for alternative treatment strategies, including antipsychotic augmentation, can be justified. Given the high prevalence of APP, it seems fair to assume that this strategy has some merit to it and that clinicians use it based on favorable outcomes in at least some of their patients. Several studies, reviews, and meta-analyses have examined the effects of APP with respect to outcomes such as efficacy, side effects, safety, and tolerability. Most researchers conclude that there is not enough evidence to support or to discourage APP.<sup>9</sup> Some studies found that APP results in superior efficacy and less rehospitalization.<sup>3,10–12</sup> Others found that APP is associated with more side effects<sup>5,13–16</sup> and nonadherence.<sup>17</sup> Conflicting conclusions have been drawn with regard to the effect of APP on mortality.<sup>18–20</sup> It is important to note that several researchers indicate that some of these results should be interpreted with caution due to methodological limitations<sup>3,21–23</sup> and that observed effects of APP, compared to monotherapy, disappear when only high-quality studies are included.<sup>9</sup> Some studies indicated positive effects for aripiprazole in combination with another antipsychotic.<sup>5,9,12,21–24</sup> Finally, clozapine tends to have superior efficacy compared with other antipsychotic agents.<sup>3,12,25</sup>

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### Clinical Points

- Antipsychotic polypharmacy (APP), although not recommended in treatment guidelines, remains a highly prevalent treatment strategy. Attempts to examine the usefulness of APP fail to include subjective experiences.
- Patient satisfaction with APP should be monitored closely. Compared to patients who use 1 antipsychotic agent, patients receiving APP may be equally happy with the efficacy but suffer more from side effects.

Results of studies evaluating the effects of adding another antipsychotic agent to clozapine are inconsistent.<sup>12,23,26</sup>

Most of the aforementioned studies examined objective clinical outcomes such as relapse, rehospitalization, side effects, and psychopathology. Obviously, these are important outcomes, but they do not necessarily correlate to patients' subjective experiences.<sup>27</sup> Consequently, we fail to include the perspective of patients and how they experience APP. This is an important omission, as experiences of side effects as well as relief from symptoms are closely related to well-being and quality of life. Consequently, the extent to which patients attribute these effects to their medication is therefore highly important for their motivation to adhere to their medication regimen.<sup>28</sup>

We found one study that examined the effects of APP on patients' treatment satisfaction. Li and colleagues<sup>29</sup> found that APP was related to a lower satisfaction with current treatment, higher quality of life in the mental domain, and more side effects. The aim of the current study is to examine the effect of APP on patients' satisfaction with pharmacologic treatment compared to antipsychotic monotherapy in a random sample of patients with a psychotic disorder.

## METHODS

### Design

Data for this article was derived from a longitudinal cohort study<sup>30</sup> we performed between 2005 and 2011 among patients with a severe mental illness (SMI) treated by the two main mental health care institutes in Amsterdam (the Netherlands), Arkin and GGZ InGeest. The objective of this study was to obtain information about quality of life, disease characteristics, general functioning, care needs, social network, inclusion in society, and victimization.<sup>30</sup> Patients were randomly selected from mental health care teams. The study was approved by the Dutch Association of Medical-Ethical Appraisal Committees (METC) for mental health organizations. For the present study, we used cross-sectional data from the assessment performed in 2011. The study was not registered at a clinical trial registry as it was not designed as a clinical trial; patients received care as usual during the study.

### Sample

Inclusion criteria for the longitudinal study were (1) a psychiatric diagnosis according to the *Diagnostic and*

*Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), (2) treatment by long-term outreaching treatment teams or in long-term clinical services, (3) a history of intensive mental health care during the previous 2 years, (4) adequate mastery of Dutch or English, and (5) residence in the Amsterdam district for at least 1 year. Exclusion criteria were being unable to understand questions or communicate, or an inability or unwillingness to give informed consent.<sup>30</sup> Of the longitudinal study sample, we selected, for this study, patients with a schizophrenia spectrum disorder (diagnosis codes 295.xx) or unspecified psychosis (diagnosis code 298.9).

In Dutch mental health care, long-term clinical services exist for patients who are not able to function in independent or sheltered housing with intensive outreaching care. Patients generally stay there for more than 1 year, and they have higher levels of therapy resistance compared to patients in long-term outreaching treatment teams.

### Assessments

For each patient, we retrieved their current medication prescription from case files. We calculated the dose equivalent for all prescribed antipsychotic medication in Defined Daily Dose (DDD) units for each patient as developed by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology.<sup>31</sup> The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO).<sup>31</sup>

We administered the Treatment Satisfaction Questionnaire for Medication (TSQM, version II)<sup>32</sup> to assess patients' satisfaction with their medication. The TSQM consists of 11 items that can be rated on a 7-point or a 5-point scale. The TSQM has 4 subscales: effectiveness, side effects, ease of use, and overall satisfaction. Atkinson et al<sup>32</sup> showed that the TSQM has good psychometric characteristics, with Cronbach  $\alpha$  ranging from 0.88 to 0.94. All data were collected in 2011.

### Statistical Analyses

All analyses were performed using SPSS Statistics for Microsoft Windows version 26. Analyses were 2-tailed with a probability level of  $P < .05$ . After calculating the daily doses, we checked for any outliers. Independent-samples  $t$  tests and  $\chi^2$  tests were performed to examine differences in antipsychotic dose, age, sex, and setting between patients who received monotherapy and those who received APP. Independent-samples  $t$  tests were also used to compare treatment satisfaction as measured with the TSQM between patients who received monotherapy and those who received APP. Finally, to examine differences in treatment satisfaction while controlling for the effects of clozapine and dose, we performed a 1-way analysis of covariance (ANCOVA) for each TSQM subscale. In these analyses, the TSQM subscale score was used as dependent variable, polypharmacy (yes/no) as independent variable, and clozapine (yes/no), daily dose, and use of a long-acting injectable (LAI) antipsychotic (yes/no) as covariates.

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**Table 1. Antipsychotic Medication Strategies in Patients With a Psychotic Disorder**

Medication Strategy	Outpatients (n = 138)		Inpatients (n = 47)		Total (N = 185)	
	n (%)	DDD, Mean (SD) <sup>a</sup>	n (%)	DDD, Mean (SD) <sup>a</sup>	n (%)	Mean (SD) <sup>a</sup>
No antipsychotic medication	10 (7.2)	...	0 (0.0)	...	10 (5.4)	...
Antipsychotic monotherapy	109 (79.0)	1.18 (0.82)	29 (61.7)	1.44 (0.49)	138 (74.6)	1.23 (0.77)
Oral medication	90 (65.2)	1.17 (0.79)	25 (53.2)	1.45 (0.51)	115 (62.2)	1.23 (0.74)
LAI	15 (10.9)	1.14 (0.91)	3 (6.4)	1.32 (–)	18 (9.7)	1.15 (0.84)
Oral and LAI medication <sup>b</sup>	4 (2.9)	1.60 (1.29)	1 (2.1)	1.33 (–)	5 (2.7)	1.55 (1.01)
Antipsychotic polypharmacy	19 (13.8)	2.40 (0.75)	18 (38.3)	1.98 (0.73)	37 (20.0)	2.21 (0.76)
Oral medication	17 (12.3)	2.45 (0.77)	12 (25.5)	2.04 (0.80)	29 (15.7)	2.29 (0.78)
Oral and LAI medication	2 (1.4)	1.94 (0.08)	6 (12.8)	1.81 (0.59)	8 (4.3)	1.85 (0.43)

<sup>a</sup>Some DDDs are based on small numbers and should be interpreted with caution. DDDs greater than 1 indicate a dosage that is higher than average. DDDs greater than 1.5 are generally classified as excessive.

<sup>b</sup>Five patients received an oral and a LAI prescription of the same agent (these were zuclopenthixol and risperidone).

Abbreviations: DDD = Defined Daily Dose, LAI = long-acting injectable.

Symbol: – = unable to calculate a meaningful SD due to small sample size.

**Table 2. Characteristics of Patients Receiving Antipsychotic Monotherapy and Polypharmacy**

Characteristic	Antipsychotic Monotherapy (n = 138)	Antipsychotic Polypharmacy (n = 37)	Total (N = 175)
Age, mean (SD), y	50.1 (9.6)	45.0 (10.8)	49.0 (10.0)
Sex, n (%)			
Male	95 (68.8)	18 (48.6)	113
Female	43 (31.2)	19 (51.4)	62
Setting, n (%)			
Outpatient	109 (79.0)	19 (51.4)	128
Inpatient	29 (21.0)	18 (48.6)	47

**Table 3. Treatment Satisfaction Questionnaire for Medication (TSQM) Scores for Patients Receiving Antipsychotic Monotherapy and Polypharmacy**

TSQM Subscale Score <sup>a</sup>	Antipsychotic Monotherapy (n = 124)	Antipsychotic Polypharmacy (n = 36)	<i>t<sub>df</sub></i>	<i>P</i>
Effectiveness	60.9 (19.9)	52.7 (19.8)	2.133 <sub>156</sub>	.034
Side effects	78.6 (24.9)	68.4 (30.5)	2.049 <sub>158</sub>	.042
Ease of use	64.0 (14.9)	61.9 (16.7)	0.714 <sub>156</sub>	.476
Overall satisfaction	59.8 (19.1)	54.6 (19.4)	1.418 <sub>163</sub>	.158

<sup>a</sup>Values are shown as mean (SD). Subscale scores on the TSQM range between 0 and 100; higher scores indicate more satisfaction with medication.

## RESULTS

We included 225 patients with SMI in the longitudinal study. For this analysis, we selected 187 patients based on diagnosis. Medication data were not available for 2 patients, resulting in a study sample of 185 patients diagnosed with schizophrenia (92.4%) or unspecified psychosis (7.6%). The majority of patients were male (63.2%), and mean (SD) age was 49.4 (10.2) years. Patients were treated in an outpatient setting (74.6%) or in long-term clinical services (25.4%). We report medication strategies separately for in- and outpatients because these populations are expected to differ with respect to severity (Table 1).

Most outpatients (79.0%) were prescribed 1 antipsychotic, and 13.8% of outpatients received more than 1 antipsychotic. A small group of outpatients (7.2%) did not receive any antipsychotic. Antipsychotic polypharmacy was more prevalent in inpatients (38.3%).

In patients who received 1 antipsychotic, the most common prescribed agents were clozapine (32.6%), olanzapine (23.2%), and risperidone (12.3%). The total number of different antipsychotics given at one time, for all in- and outpatients who were given APP treatment, was 2. In half of those cases, this involved a combination with clozapine. The most commonly prescribed agents in patients who received 2 antipsychotics were clozapine (51.4%), aripiprazole (35.1%), olanzapine (29.7%), haloperidol (21.6%), risperidone (18.9%), and zuclopenthixol (13.5%). The most commonly prescribed combination of antipsychotics in our sample was clozapine with aripiprazole

(21.6%). The LAI antipsychotics chiefly prescribed in our sample were risperidone (36.7%), zuclopenthixol (26.7%), and haloperidol (16.7%). Other LAI antipsychotics such as bromperidol, paliperidone, fluphenazine, and flupentixol were prescribed in 1 or 2 patients each. Daily dose in patients who received 2 antipsychotics was considerably higher ( $P < .001$ ) compared to that in monotherapy patients.

Patients who received polypharmacy were, in comparison with patients who received monotherapy, on average 5 years older ( $t = 2.822$ ;  $P = .011$ ) and more often female ( $P = .023$ ). Polypharmacy was utilized more among patients who were staying in a nonacute psychiatric ward ( $P = .001$  Table 2).

Patients with monotherapy reported higher levels of satisfaction on the domains of effectiveness and side effects. Patients who needed to take 2 antipsychotics each day did not rate the ease of use differently compared to those who took 1 antipsychotic. There was also no difference in overall satisfaction with medication (Table 3).

Previous studies that examined effects of antipsychotic polypharmacy showed that results are influenced by the use of clozapine.<sup>10,24,33</sup> Also, dosage is known to have an effect on effectiveness and side effects. Finally, although inconclusive, the use of LAI antipsychotics may affect medication effectiveness.<sup>34,35</sup> We therefore performed a 1-way ANCOVA to determine the differences in TSQM subscale scores between patients receiving 1 and 2 antipsychotic agents, controlling for the use of clozapine, prescribed daily dosage, and the use of LAI antipsychotics (Table 4). We found that the use of clozapine was related

**Table 4. ANCOVA Results for the Effect of Antipsychotic Polypharmacy on Treatment Satisfaction Questionnaire for Medication (TSQM) Scores Controlling for the Effects of Clozapine, Antipsychotic Dose, and the Use of a Long-Acting Injectable (LAI) Antipsychotic**

Dependent Variable (TSQM Subscale Score)	df	Main Effect (Polypharmacy)		Covariate					
				Clozapine		Antipsychotic Dose (DDD)		LAI Antipsychotic	
		F	P	F	P	F	P	F	P
Effectiveness	142	1.924	.168	1.56	.213	1.56	.213	3.16	.078
Side effects	143	9.744	.002	4.96	.028	1.13	.290	0.31	.580
Overall satisfaction	147	0.778	.379	0.37	.542	0.423	.516	5.20	.024

Abbreviations: ANCOVA = analysis of covariance, DDD = Defined Daily Dose.

to higher satisfaction with side effects ( $B = 10.02$ ). Antipsychotic dose was not related to any of the TSQM subscales. Patients who used an LAI antipsychotic had lower overall medication satisfaction ( $B = -0.95$ ) and, on a trend level, were less satisfied with effectiveness ( $B = -0.79$ ). After controlling for the effects of clozapine, dose, and the use of LAI antipsychotics, we found no more differences between patients receiving APP and those receiving monotherapy on effectiveness. Difference between the groups on perceived side effects remained significant after controlling for clozapine, dose, and the use of LAI antipsychotics ( $B = 18.00$ ). In additional analyses, we found lower satisfaction, as measured with version II of the TSQM, on the items that assess the interference of side effects with physical health, ability to function, mood, or emotions, but in particular on the item referring to interference with mental functioning. The subscale ease of use was excluded from this analysis because we had no hypothesis on the influence of clozapine or dosage on that variable.

## DISCUSSION

We found that APP is common in our sample of in- and outpatients with a psychotic disorder. Among outpatients, 14% received 2 different antipsychotic agents; in inpatients, more than a third (38%) received 2 different antipsychotics. This is consistent with findings in other studies.<sup>5-7</sup> Polypharmacy is accompanied by a considerably higher mean dosage of 2.21 DDD, which may even be classified as excessive. Also, dosage is known to have an effect on effectiveness and side effects.

So far, we do not know the effects of polypharmacy and whether or not it is a suitable treatment strategy in specific cases. Most studies have focused on objective outcome parameters. In this study, we examined subjective experiences of patients with medication.

We found that patients who use clozapine are more satisfied with side effects, and those who use an LAI antipsychotic have lower overall medication satisfaction. After controlling for the effects of clozapine, antipsychotic dose, and the use of LAI antipsychotics, we found that patients who receive 2 antipsychotics are less satisfied concerning the side effects of their medication in comparison with patients who receive antipsychotic monotherapy. This is in line with the results

of Li et al,<sup>29</sup> who found more side effects among APP users. We do not know if this difference is caused by increased severity of side effects or if augmentation strategies add to the number of side effects. A previous study<sup>36</sup> showed that polypharmacy likely increases the number of side effects. This is an important finding, as subjective side effects are associated with poor adherence.<sup>28,37</sup> The lower satisfaction with side effects was not caused by the relatively high dosage found in patients receiving APP, as we found no association between dosage and scores on any of the TSQM subscales. Patients were, in comparison with patients treated with 1 antipsychotic, most dissatisfied with the interference of side effects on their mental functioning.

Patients in both groups were equally satisfied with the efficacy of their medication. This is an interesting finding if we assume that the majority of APP patients showed inadequate antipsychotic response when treated with 1 agent. Treated with 2 antipsychotic agents, they rate the effectiveness of their medication just as high as other patients, which may indicate that APP seems to work.

A limitation of this study is that data were collected in 2011, now 10 years ago. Polypharmacy is, however, still common, and therefore these data are relevant to further our understanding of the effects of APP for patients. Nevertheless, prescription patterns may have changed since then. For instance, it is likely that the use of so-called second-generation LAI antipsychotics has increased since we performed our study. First-generation LAI antipsychotics, although not a homogeneous class,<sup>38</sup> can have different side effect profiles<sup>39</sup> and also may be prescribed to patients with different characteristics.<sup>39,40</sup> Therefore, our results concerning medication satisfaction of LAI antipsychotic users should be interpreted with caution. Another limitation is that some patients who were prescribed 2 antipsychotics may have been in the process of changing from one agent to another. In those cases, APP is only temporary. Unfortunately, this information was not available to us. Due to the sample size of our study, we did not differentiate between the different combinations of antipsychotics. Also, we were unable to control for the use of anticholinergics or other psychotropic medication.

We found that subjective effectiveness, ease of use, and overall satisfaction with medication are not different for patients who receive 1 or 2 antipsychotics. This result seems



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encouraging for those patients who show poor response to other treatment strategies; it does, however, seem to come at a price of less favorable perceived side effects. Therefore, tolerability of side effects should be closely monitored and discussed with the patient to assure the treatment is acceptable and patients remain motivated. We recommend

future studies to further examine the subjective effectiveness and tolerability of polypharmacy. A way forward may be to examine specific, often-used combinations such as clozapine plus aripiprazole. Doing so may contribute to developing guidelines concerning patient characteristics, risks, and benefits for the use of specific combinations.

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**Editor's Note:** We encourage authors to submit papers for consideration as a part of our Focus on Psychosis section. Please contact Ann K. Shinn, MD, MPH, at ashinn@psychiatrist.com.