Attitudes Toward Medications and the Relationship to Outcomes in Patients with Schizophrenia

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Abstract

The determinants of attitudes toward medication (ATM) are not well elucidated. In particular, literature remains equivocal regarding the influence of cognition, adverse events, and psychiatric symptomatology. This study evaluated relationships between those outcomes in schizophrenia and ATM. This is a retrospective analysis of data collected during the Texas Medication Algorithm Project (TMAP, n=307 with schizophrenia-related diagnoses), in outpatient clinics at baseline and every 3 months for ≥1 year (for cognition: 3rd and 9th month only). The Drug Attitude Inventory (DAI-30) measured ATM, and independent variables were: cognition (Trail Making Test [TMT], Verbal Fluency Test, Hopkins Verbal Learning Test), adverse events (Systematic Assessment for Treatment-Emergent Adverse Events, Barnes Akathisia Rating Scale), psychiatric symptomatology (Brief Psychiatric Rating Scale, Scale for Assessment of Negative Symptoms [SANS]), and medication adherence (Medication Compliance Scale). Analyses included binary logistic regression (cognition, psychiatric symptoms) and chi-square (adverse events, adherence) for baseline comparisons, and linear regression (cognition) or ANOVA (adverse events, adherence) for changes over time. Mean DAI-30 scores did not change over 12 months. Odds of positive ATM increased with higher TMT Part B scores (p=0.03) and lower SANS scores (p=0.02). Worsening of general psychopathology (p<0.001), positive symptoms (p<0.001), and negative symptoms (p=0.007) correlated with negative changes in DAI-30 scores. Relationships between cognition, negative symptoms, and ATM warrant further investigation. Studies evaluating therapies for cognitive deficits and negative symptoms should consider including ATM measures as endpoints. Patterns and inconsistencies in findings across studies raise questions about whether some factors thought to influence ATM have nonlinear relationships.

Key Words: Schizophrenia, Schizoaffective Disorder, Drug Attitude Inventory, Antipsychotic, Outcomes

Introduction

For patients with schizophrenia, non-adherence is common (objective estimates range from 41–57%) (1-4), and strongly associated with symptom exacerbation, relapse, more frequent psychiatric hospitalizations, and longer psychiatric inpatient stays (5-7). Medication adherence is often closely related to a patient's attitudes toward medications (ATM). For schizophrenia, this relationship has been demonstrated with the Drug Attitude Inventory (DAI-30), which was developed to assess overall attitudes about health and medications in patients with schizophrenia. Higher scores on the DAI-30 are predictive of adherence to antipsychotics (8, 11). Understanding the factors that influence ATM can help clinicians to better address patient-specific barriers to adherence.

Studies have shown that ATM in schizophrenia may be influenced by myriad factors, including psychopathology, sociodemographic characteristics, and environmental stimuli, but there is still much to learn about the determinants of

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Submitted: October 31, 2014; Revised: February 13, 2015; Accepted: March 5, 2015

Clinical Implications

A more complete understanding of factors that influence attitudes toward medications (ATM) and adherence can inform strategies for improving overall outcomes in schizophrenia. Consistent with prior studies, we found ATM to be correlated with executive dysfunction (specifically measured via TMT Part B) and negative symptoms (which may themselves be interrelated). It may be that patients with more severe frontal lobe dysfunction and/or negative symptomology are less able to recognize the severity or impact of their illness and appreciate the need for medication. Although antipsychotic medications have not yielded substantive improvements to cognition, adjunctive therapies are being explored. Including measures of ATM and adherence in those studies could provide further valuable insights.

We found no relationship between adverse events and ATM or between ATM and adherence, perhaps due to sample characteristics (i.e., low adverse event severity and overwhelmingly positive ATM). These results, along with findings from prior literature, raise the question of whether factors that influence ATM act in a linear fashion. It is possible that the relationship between adverse events could be mediated by severity, while the relationship between ATM and adherence may be stronger with more negative ATM. It may be worthwhile for future studies of ATM to consider nonlinear models. Better understanding of factors that influence ATM and treatment adherence in patients with schizophrenia may lead to improvements in quality of life, functionality, and overall outcomes.

ATM. Results are conflicting or inconclusive regarding the influence of adverse events, psychiatric symptomatology, and cognitive functioning, indicating the need for further investigation. Studies of adverse events and ATM are divided between those reporting significant correlations (10, 12-15) and those finding no relationship (16-18). Results are also mixed for ATM and psychiatric symptom severity. Some studies find no relationship between either general psychopathology or positive symptom severity and ATM (19, 20), while others have reported significant relationships between positive and negative symptoms of schizophrenia and ATM (16-21). Cognitive performance has been positively correlated with ATM, but few studies have investigated this relationship and, as with other factors, findings are inconsistent (18-22).

This study was undertaken to learn more about the relationship of these factors with ATM using data collected in Phase 3 of the Texas Medication Algorithm Project (TMAP). The specific objectives were to examine relationships between DAI-30 scores and: 1) cognition, 2) adverse events, 3) psychiatric symptomatology, and 4) medication adherence.

Materials and Methods

Subjects

This is a retrospective secondary analysis of data collected in TMAP Phase 3 (23). TMAP was initiated to develop and evaluate implementation of cost-effective, "standard-of-care" guidelines for the treatment of mental illnesses (24). The three phases of TMAP were: 1) algorithm development, 2) feasibility evaluation for algorithm use in clinical practice, and 3) prospective controlled evaluation of clinical and economic outcomes of the algorithms. TMAP Phase 3 included 465 patients with schizophrenia-related *DSM-IV* diagnoses, excluding schizoaffective disorder, bipolar type. Patients were adult (≥18 years) outpatients with at least one follow-up visit and able to provide written informed consent. Exclusion criteria were minimal: diagnosis of mental retardation, need for acute substance detoxification, or enrollment in an Assertive Community Treatment (ACT) program (in which intensive mental health services provided could confound study results) (23).

Patients were recruited from a non-randomly selected clinic population included in TMAP, which offered either algorithm-driven disease management (ALGO, n=165) or treatment as usual (TAU, n=142). Subjects who were enrolled in the treatment as usual at an algorithm clinic (TAUinALGO, n=156) arm during Phase 3 were excluded from our analyses (23). Each clinic offering ALGO was also considered to be a TAUinALGO site for one of the other two disorders not treated according to the algorithm (i.e., patients with bipolar disorder or major depressive disorder treated at the ALGO schizophrenia clinics) (23). It was hypothesized in TMAP that the TAUinALGO patients would have better outcomes than patients enrolled in a TAU-only clinic. Patients entered the study if their physicians determined a need for antipsychotic medication switching to address adverse events and/or insufficient symptom improvement. To offset the low frequency of medication changes in the TAU group, patients could also enroll if their latest Brief Psychiatric Rating Scale (BPRS) scores were within one standard deviation of the mean for the ALGO group. In both groups, participation was limited to 24 months.

Dependent Variable

The dependent variable in this study was total DAI-30 score. The DAI-30 is a validated 30-item self-report questionnaire developed to estimate ATM in schizophrenia by assessing patients' perceptions of their medication, as well

as their sense of well-being while on medication (8). DAI-30 total scores range from +30 to -30, with overall positive scores indicating subjectively positive ATM and negative scores indicating subjectively negative ATM (8). This study included DAI-30 scores collected at baseline, 6 months, and 12 months. For analyses, both continuous (i.e., total) and dichotomized (i.e., positive attitude/positive total score or negative attitude/negative total score) scores were used.

Independent Variables

Independent variables were cognition, adverse events, psychiatric symptoms, and medication adherence. *Cognition* was evaluated using the Brief Cognitive Assessment (BCA) battery, which comprises the Trail Making Test (TMT) Parts A and B, the Verbal Fluency Test (VFT), and the Hopkins Verbal Learning Test (HVLT). The BCA was developed by TMAP researchers to meet clinicians' needs for ease of use, while still providing measurements that are valid, sensitive to treatment effects, reflective of all relevant cognitive domains, and related to functional outcomes in patients with schizophrenia (25). There were no a priori hypotheses about relationships between DAI-30 parameters of cognition. This study included BCA scores collected at baseline, 3 months, and 9 months.

The TMT is a reliable and valid two-part (A and B) inventory assessing general mental ability, processing speed, and attention. Both parts are timed and are scored based on total time required to complete, while accounting for errors (26). The VFT assesses speed and flexibility of verbal thought processes (27). TMAP Phase 3 used the letters and object categories versions of the VFT. The score for each letter or object category is the total number of appropriate words the subject named. The HVLT is a reliable and valid measure of cognition assessing verbal learning and memory, scored based on the total number of words recalled from a list read aloud (28). Two parts (Free Recall and Recognition) of the HVLT were used in TMAP Phase 3. Scores for each cognitive test were converted into z-scores and averaged for a global cognitive function z-score.

Adverse events were assessed using modified versions of the Systematic Assessment for Treatment-Emergent Adverse Events (SAFTEE) and the Barnes Akathisia Rating Scale (BARS). The SAFTEE is a comprehensive, clinician-administered review of systems with body system-specific questions about adverse events since the last visit (29). TMAP used the 23-item SAFTEE with "Yes"/"No" responses, and one global side-effect burden item with a 4-point scale (0=no adverse events, 4=adverse events so severe I had to be hospitalized). The BARS is a reliable, valid, 4-item instrument that assesses for drug-induced akathisia; total scores range from 0–14, and scores ≥2 are indicative of akathisia (30). This study included adverse event data collected at baseline and 6 months.

Psychiatric symptoms were measured with the Brief Psychiatric Rating Scale (BPRS-18) and the Scale for the Assessment of Negative Symptoms (SANS). BPRS is an 18-item assessment of general psychiatric symptom severity in schizophrenia (31). Items are rated on a 7-point scale (1=not present, 7=extremely severe), with total scores ranging from 18–126 (31). TMAP evaluated positive symptom severity with the BPRS positive item subscale (sum of conceptual disorganization, hallucinatory behavior, unusual thought content, and suspiciousness items). SANS rates negative schizophrenia symptoms (e.g., alogia, avolition, anhedonia) using 25 items on a 6-point scale (0=no negative symptoms present, 5=severe negative symptomatology), with total scores ranging from 0–125 (32). This study included psychiatric symptom scores collected at baseline and 6 months.

Medication adherence was evaluated with the Medication Compliance Scale (MCS), a reliable, valid, 4-item ("Yes"/"No") self-report measure of adherence (33). Medication-taking behaviors are assessed at several time points (i.e., yesterday, past week, past month, past three months) (33). For this study, adherence categories were: 0=high, 1–2=medium, 3–4=low. This study included adherence data collected at baseline and 6 months.

Data Collection and Analyses

Data for this study were collected retrospectively from the original TMAP study, in which assessments were collected at baseline and every 3 months for at least 1 year (except for cognition, which was assessed at baseline, 3 months, and 9 months). All statistical tests were two-tailed, with a significance level of α=0.05. Statistical analyses were performed using SPSS® Version 14.0 for Windows.

T-tests and chi-square analyses were used to compare baseline characteristics between the two groups. Changes in continuous DAI-30 scores from baseline to 6 and 12 months were examined using paired-samples t-tests. To examine the relationship between cognitive function and ATM, baseline dichotomized DAI-30 scores were regressed on z-scores for each baseline cognition measure (TMT Parts A and B, VFT letters and object categories, and HVLT), followed by the combined z-score for all measures of cognition in six separate binary logistic regression models. The relationship between changes in cognition (baseline to 3 months and baseline to 9 months) and changes in ATM (continuous DAI-30) (baseline to 6 months and baseline to 12 months) was examined using linear regression. Covariates in each regression model included: group (ALGO vs. TAU), baseline BPRS-18 score, baseline SANS score, age, length of illness, and education.

Table 1 Comparison of Baseline Demographic Characteristics of Patients with a Schizophrenia-Related Diagnosis by Group

Characteristic	ALGO (N=165)	TAU (N=142)	Statistic (df)	p-value
Age, mean±SD (yrs)	40.6±10.7	41.2±10.5	t (303)=-0.54	0.59
Male, number (%)	101 (61.2)	93 (65.5)	$\chi^2(1)=0.60$	0.44
Race/Ethnicity, number (%)				
Hispanic	85 (51.5)	70 (49.3)	$\chi^2(3)=5.18$	0.16
Caucasian	49 (29.7)	53 (37.3)		
African American	30 (18.2)	16 (11.3)		
Other	1 (0.6)	3 (2.1)		
Education, mean±SD (yrs)	10.7±3.0	10.8±3.2	t (302)=-0.21	0.83
Marital Status, number (%)				
Never Married	91 (55.2)	86 (60.6)	χ^2 (4)=3.75	0.44
Divorced	33 (20.0)	24 (16.9)		
Married	26 (15.8)	14 (9.9)		
Separated	9 (5.5)	11 (7.7)		
Widowed	4 (2.4)	5 (3.5)		
Employment				
Unemployed	140 (84.8)	114 (80.3)	χ^2 (2)=0.33	0.85
Part-Time	16 (9.7)	13 (9.2)		
Full-Time	7 (4.2)	4 (2.8)		
Length of Illness, mean±SD (yrs)	15.8±10.8	18.7±11.2	t (305)=-2.31	**0.02**
Age of Illness Onset, mean±SD (yrs)	24.9±9.1	22.5±9.8	t (303)=2.18	**0.03**
BPRS-18 scores, mean±SD	38.7±11.2	45.4±10.7	t (305)=-5.31	**<0.001**
SANS scores, mean±SD	14.1±4.8	13.2±5.0	t (302)=1.60	0.11
Schizoaffective disorder dx (not bipolar), number (%)	46 (27.9)	40 (28.2)	$\chi^2(1)=0.003$	0.96
General Medical Conditions, number (%)				
None	72 (43.6)	80 (56.3)	$\chi^2(3)=5.22$	0.16
1	45 (27.3)	30 (21.1)		
2	24 (14.5)	14 (9.9)		
3+	24 (14.5)	18 (12.7)		

ALGO=algorithm-guided treatment; TAU=treatment as usual; SD=standard deviation; yrs=years; dx=diagnosis

Table 2 Paired T-Test Comparison of Change in Drug Attitude Inventory Scores from Baseline to 6 and 12 Months

Group		DAI Baseline Mean±SD	DAI 6 months Mean±SD	t [df]	p-value
Overall	(N=246)	16.5±10.2	17.3±10.2	-1.13 [245]	0.26
ALGO	(N=136)	16.8±10.2	17.1±10.6	-0.31 [135]	0.76
TAU	(N=110)	16.1±10.1	17.5±9.8	-1.52 [109]	0.13
Group		**DAI Baseline Mean±SD**	**DAI 12 months Mean±SD**	**t [df]**	**p-value**
Overall	(N=219)	17.6±9.8	18.3±9.8	-0.99 [218]	0.32
ALGO	(N=115)	17.5±9.8	18.9±10.5	-1.64 [114]	0.11
TAU	(N=104)	17.8±9.8	17.5±8.9	0.26 [103]	0.80

DAI=Drug Attitude Inventory; SD=standard deviation; df=degrees of freedom; ALGO=algorithm-driven treatment; TAU=treatment as usual

Associations between adverse events (tolerable or intolerable, present or absent) and dichotomized DAI-30 were assessed with chi-square tests, and one-way ANOVA was used to detect whether changes in side-effect burden were associated with changes in continuous DAI-30 scores.

The relationship between psychiatric symptom severity (BPRS-18 and SANS scores) and dichotomous DAI-30 scores was examined with logistic regression. The relationship between change in psychiatric symptomatology and change in continuous DAI-30 scores (from baseline to 6 months) was evaluated with linear regression, controlling for group (ALGO vs. TAU) and baseline covariates (employment status, length of illness, self-reported adherence, family history of mental illness, global side-effect burden, and number of medical comorbidities).

Associations between dichotomous DAI-30 scores and adherence (high, medium, low) were assessed with chi-square tests, and one-way ANOVA was used to detect associations between changes in adherence and changes in continuous DAI-30 scores.

Results

A total of 307 adults with a schizophrenia-related diagnosis (excluding schizoaffective disorder, bipolar type) enrolled in either the ALGO or TAU arms in Phase 3 of TMAP were included. There were no significant differences in socioeconomic characteristics between the algorithm-driven disease management (ALGO, n=165) or treatment as usual (TAU, n=142) groups, but the TAU group had a more severe clinical profile (earlier age of onset, longer length of illness, higher BPRS scores) (see Table 1). At baseline, mean DAI-30 scores for both groups ranged from 16-18, indicating mostly positive ATM, and did not change significantly at 6 or 12 months (see Table 2). At all observation points (baseline, 6 months, and 12 months), the majority of subjects (≥70%) reported positive ATM.

DAI-30 scores were not significantly related to z-scores on the TMT Part A at baseline (OR=1.09; 95% CI: 0.72–1.64, p=0.69), but the odds of having positive ATM were 1.64 times higher for each unit increase in TMT Part B z-score at baseline (OR=1.64; 95% CI: 1.06–2.55, p=0.03). No association was found between ATM and VFT letters (OR=0.82; 95% CI: 0.50–1.34, p=0.43) or object categories (OR=1.08; 95% CI: 0.65–1.80, p=0.76) tests, or the HVLT (OR=1.01; 95% CI: 0.65–1.57, p=0.98), nor were scores on the combined cognitive battery related to ATM (OR=1.19; 95% CI: 0.77–1.83, p=0.44) at baseline, after controlling for covariates. No relationship was found between interim change in DAI-30 score (baseline to 6 months) and combined cognitive z-scores (baseline to 3 months) (β=-0.06; 95% CI: -2.76–1.16, p=0.42), or between final change in DAI-30 scores (baseline to 12 months) and combined cognitive z-scores (baseline to 9 months) (β=0.08; 95% CI: -0.91–2.84, p=0.31). In this sample, patients who performed better on the TMT Part B had more positive ATM, while scores on TMT Part A, VFT (letters and object categories), HVLT, and the combined cognitive battery had no relationship with ATM. Observed longitudinally, changes to global cognition (the combined cognitive battery) were unrelated to changes in ATM over time.

No associations were found between DAI-30 scores and side-effect burden (tolerable or intolerable) at baseline (χ^2=0.22, df=1, p=0.64) or at 6 months (Fisher's exact test, p=1.00), or with drug-induced akathisia at baseline (χ^2=0.02, df=1, p=0.89) or at 6 months (χ^2=0.27, df=1, p=0.60). Similarly, changes in side-effect burden from baseline to 6 months (F[2,239]=1.36, 95% CI: -0.64–2.04, p=0.26) were unrelated to changes in DAI-30 scores.

Table 3 Linear Regression Models Analyzing the Relationship Between Changes in Psychiatric Symptomatology and Changes in Attitudes Toward Medications from Baseline to 6 Months*

Measure of Psychiatric Symptom Severity	Unstandardized Coefficients		Standardized Coefficients	t	p-value	95% CI
	b	Std. Error	β			
General psychopathology						
Intercept	-0.25	6.25	—	-0.04	0.97	-12.57 – 12.07
Change in BPRS-18 Total Score	-0.24	0.06	-0.06	-4.18	**<0.001**	-0.35 – -0.13
Intercept	-2.95	6.32	—	-0.47	0.64	-15.40 – 9.50
Change in BPRS-18 Positive Item Subscale Score	-0.51	0.13	0.08	-3.81	**<0.001**	-0.78 – -0.25
Intercept	-1.34	6.53	—	-0.21	0.84	-14.21 – 11.52
Change in SANS Score	-0.34	0.13	-2.74	-2.74	**0.007**	-0.63 – -0.10

std.=standard; CI=confidence interval; BPRS-18=18-item Brief Psychiatric Rating Scale; SANS=Scale for the Assessment of Negative Symptoms

*Covariates in each of the regression models included: group (ALGO [algorithm-driven treatment] vs. TAU [treatment as usual]), employment status, length of illness, self-reported medication compliance at baseline, family history of mental illness, global side-effect burden at baseline, and number of medical comorbidities at baseline.

No relationship was found between DAI-30 scores and general psychiatric symptom severity at baseline, as measured by overall BPRS-18 (β=-0.03; 95% CI: 0.94–1.01, p=0.09) or between DAI-30 and positive psychiatric symptom severity, measured by the BPRS positive-item subscale (β=-0.03; 95% CI: 0.90–1.06, p=0.53). There was, however, a significant relationship between changes from baseline to 6 months in DAI-30 scores and changes to both overall BPRS-18 scores (p<0.001) and positive-item subscale scores (p<0.001) after controlling for covariates (see Table 3). The findings suggest that, as either general psychopathology or positive symptoms worsen over time, ATM also worsens. At baseline, negative psychiatric symptom severity was inversely related to ATM; for each one point increase on the SANS (indicating more severe negative symptoms), the odds of having positive ATM were 0.1 times lower (β=-0.11; 95% CI: 0.82–0.98, p=0.02). Longitudinally (baseline to 6 months), changes in SANS scores correlated significantly with changes in ATM, after controlling for covariates (p=0.007), indicating that as negative symptom severity worsens over time, ATM will also worsen (see Table 3).

No association was observed between medication adherence and DAI-30 score at baseline (χ^2=0.37, df=2, p=0.83) or at 6 months (χ^2=1.16, df=2, p=0.56). Longitudinally (baseline to 6 months), changes in reported adherence (no change, improved adherence, worsened adherence) were not related to changes in DAI-30 scores (F[2,242]=0.63, p=0.53).

Discussion

The population evaluated in this study is a "real-world" sample of patients with schizophrenia-related diagnoses who are typically seen in outpatient Mental Health and Mental Retardation (MHMR) clinics across the state of Texas. A high percentage of these patients were middle-aged, Hispanic (>50%), unemployed (>80%), low-income (mean disposable monthly income between $255 and $440) (34).

Cultural factors are well known to influence medication-taking behaviors and experiences, which is important to consider when comparing our results with studies that have examined similar outcomes. For example, non-medical factors, such as spirituality and religion, have been shown to influence Hispanic patients' attitudes toward medication and medication-taking behaviors (35, 36). Additionally, a secondary analysis of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) data showed that response to medications, side-effect burden, and medication-related quality of life differed between African-American, Hispanic, and non-Hispanic white patients with schizophrenia (37).

Cognition and ATM

In the current study, a significant relationship was found between less time required to complete the TMT Part B and positive attitudes toward psychotropic medications. No significant relationship was observed for other measures of cognition and ATM or for the combined cognitive battery. No relationship was observed between changes in cognition and changes in ATM over time. TMT Part B is considered a useful indicator of general frontal lobe dysfunction and cognitive flexibility (38, 39), and neuroimaging studies of patients with schizophrenia have confirmed correlations between poor performance on TMT Part B and reduced perfusion and metabolism in regions of the prefrontal cortex associated with executive function (40, 41). Thus, the correlation observed in this study between TMT Part B performance and ATM suggests that deficits in executive function observed in schizophrenia may play a role in ATM.

Other studies evaluating relationships between cognition and ATM have shown mixed results. Variation in methods, analysis, and measures used, including whether global cognitive scores versus individual subdomains were assessed, clouds interpretation. Kim and colleagues did not find a significant relationship between ATM and TMT; however, it was not specified whether the TMT total score or the score of the individual parts (A and B) was used (18). Parts A and B of the TMT are generally analyzed separately, as they measure different constructs. The Kim study also reported a significant relationship between ATM and the Wisconsin Card Sorting Test (18)—another measure of prefrontal cortical activity (42)—but not global measures of cognition (18). Similarly, Goodman and colleagues found ATM to be strongly correlated with prefrontal activity (e.g., planning and judgment), but not other cognitive domains (22).

Brain and colleagues found more negative ATM, but not cognitive performance, to be predictive of non-adherence to psychotropic medications; however, their study utilized a composite neurocognitive battery versus results of individual tests of cognition (43). Boyer and colleagues found that "awareness" of positive and negative symptoms in schizophrenia was strongly related to two measures of neurocognition: the California Verbal Learning Test (measure of memory) and the VFT (category domain only), which in turn influenced non-adherence (44). In their study, only insight was significantly correlated with ATM, not cognition or psychiatric symptoms (44). The authors propose that poor insight be regarded as an inability to be able to self-identify symptoms and illness as a consequence of neurocognitive deficits and negative symptoms in schizophrenia (44). Their statistical models suggest a complex, nonlinear relationship between neurocognition, insight, ATM, and adherence, which the authors suggest might account for some of the contradictory results in earlier studies measuring similar variables (44). Despite the differences in methodology between these studies, the consistent finding of a relationship between prefrontal cognitive deficits in schizophrenia and ATM warrants further investigation. Cognitive deficits in patients with schizophrenia may play a meaningful role in

their ability to recognize the benefits of antipsychotic treatment (44-48), which may, in turn, influence ATM (44-49).

Symptoms and ATM

We found a relationship between higher negative symptom severity at baseline and more negative ATM, but severity of positive symptoms and general psychopathology did not influence ATM at baseline in the TMAP population. We also found that worsening general psychopathology, positive symptoms, and negative symptoms were associated with more negative ATM from baseline to 6 months, yet mean DAI-30 scores for the total population did not change over time. Studies that have found ATM to be correlated with severity of positive symptoms and general psychopathology differ from ours in notable aspects. Adewuya and colleagues included only subjects taking first-generation antipsychotics (FGAs) (versus primarily second-generation antipsychotics [SGAs] in this study) (21), while subjects studied by both Hofer and Rocca exhibited relatively low or moderate positive symptom severity (compared to our moderately severe patient population) (13, 46). Of note, the Rocca study observed ATM to be higher in subjects taking SGAs (46). It is possible that the relative predominance of SGA use in the TMAP study had a confounding effect. On the other hand, Freudenreich and colleagues found no difference in DAI-10 scores between antipsychotic classes (SGA vs. FGA); however, they did report a significant correlation between ATM and symptom severity in all categories (negative, positive, and general psychopathology) (16). As in our study, Freudenreich used the SANS to assess for negative symptoms, while general psychopathology and positive symptoms were measured with the Positive and Negative Syndrome Scale (PANSS); whereas TMAP used the BPRS (16). The differences in study findings may be attributable, in part, to differences in assessment methods or population studied (70% white, non-Hispanic subjects in their study) (16).

None of the aforementioned studies evaluating psychiatric symptom severity assessed the relationship between change in ATM over time with symptom change over time. Sajatovic and colleagues found that while psychiatric symptoms and insight improved significantly over the course of a short inpatient hospitalization (average length of stay 12.7 days), ATM did not (50). A study by Lee and colleagues found ATM did not significantly change over a 48-week period of time in subjects taking long-acting injectable risperidone treatment despite significant improvement in PANSS subscale scores (51). Docherty and colleagues found significantly improved ATM only for patients achieving remission from psychiatric symptoms based on overall PANSS scores at 6 months (52). Thus, remission from bothersome psychiatric symptoms could potentially lead to improved ATM.

In addition to our study and that of Freudenreich, Adewuya and colleagues reported a relationship between higher negative symptom severity and more negative ATM (16, 21). Conversely, Boyer and colleagues did not find "awareness" of positive or negative symptoms (measured via the Scale to Assess Unawareness of Mental Disease [SUM-D]) to be significantly correlated with ATM; however, negative symptoms of schizophrenia reduced personal recognition of symptoms and illness (44). Neuroimaging and clinical studies have shown that negative symptoms in schizophrenia are related to frontal lobe deficits, particularly impaired executive function (see Orellana and Slachevsky [2013] for a comprehensive review) (53). As noted earlier, deficits in prefrontal cognition may be associated with more negative ATM in patients with schizophrenia. As antipsychotic medications do not tend to offer substantial improvement in negative or cognitive symptoms of schizophrenia, use of agents specifically aimed at these symptoms are of great interest in schizophrenia research. Agents that modulate NMDA glutamatergic receptors, glycine transporters, nicotinic α-7 receptors, and several other novel targets, are showing promise for improving cognition and negative symptoms in patients with schizophrenia (54, 55). It may be useful to include measures of ATM in future trials of these adjunctive pharmacotherapies, as a correlate of improved cognition as well as a valuable end-point in its own right. Psychoeducation may also yield improvements to ATM, especially if interventions are targeted toward improving self-awareness and perceived need for medication (56, 57).

Adverse Events and ATM

Consistent with some studies (16, 20), but in contrast to others (12, 13, 21), we found no significant relationship between ATM and adverse events from antipsychotic medications. Substantial heterogeneity in methodology and patient characteristics among these studies has yielded considerably inconsistent findings, but some commonalities have surfaced. Sedation, extrapyramidal symptoms (EPS), and metabolic side effects often cause substantial distress (13, 21, 58, 59), even if no correlation with ATM is found (60). Additionally, employment is associated with less positive ATM in studies that found (13, 21), and did not find (16), correlations between adverse events and ATM. As suggested by Adewuya and colleagues, the interference of adverse events, especially sedation and extrapyramidal syndrome, in the workplace may foster more negative ATM in employed patients (21). Although this hypothesis was not assessed in the current study, it is not incompatible with our findings, as over 80% of subjects in TMAP were unemployed and >80% reported positive ATM.

Another commonality is that study groups using SGAs often report higher mean ATM scores (13, 15, 58, 59, 61) than those using primarily FGAs (21, 59, 61). The literature remains equivocal on comparisons of FGAs and SGAs, but because there is less risk of EPS with SGAs, their introduc-

tion was met with hope for improved subjective response, ATM, and adherence. Sedation and metabolic side effects, however, have proven to be burdensome (62), and independently associated with more negative ATM (15, 58, 59). Notwithstanding, Garcia-Cabeza and colleagues found a correlation between ATM and EPS, irrespective of medication class (63). Moreover, a recent comparison by Karthik and colleagues of ATM by medication class, found more positive ATM in the SGA group, with the principle correlates of ATM being side-effect severity (rather than type) and insight (59). In the TMAP population, over 85% of subjects used SGAs, and only 20% of subjects reported adverse events to be intolerable at baseline (only 10% at 6 months). The majority of subjects (>80%) reported positive ATM at baseline; and 90% reported positive ATM at 6 months. It is plausible that the high prevalence of SGA use and low prevalence of severe adverse events may have minimized any relationship between adverse events and ATM in our study. In addition, as suggested by Hofer and colleagues, close management of study subjects by specialized mental health clinicians may have had a modifying effect (13).

ATM and Adherence

Contrary to previous studies, we did not find a significant relationship between medication adherence and ATM (10, 11, 64, 65). Drug attitudes are multi-factorial composites of perceived medication effects, insight, health, and well-being. Conceivably, some factors may correlate more than others with adherence. Using the Rating of Medication Influences to measure ATM, Mutsatsa and colleagues found adherence to be related to negative, but not positive, ATM subscores (64). Similarly, in a study of antidepressant use among mixed psychiatric outpatients, De las Cuevas, Peñate, and Sanz found adherence related to total DAI-30 score, but to only one subscale of the Beliefs about Medicines Questionnaire: "Harm" (66). In our study, with overall positive ATM and no subscore analyses, relationships between adherence and negative ATM or ATM subfactors—if any existed—might not have been detected. In the study by Brain and colleagues using DAI-10 total scores, non-adherent patients had a significantly more negative ATM (6.2) compared to adherent patients (2.4); however, non-adherent patients still had a "positive" attitude overall (43). In contrast to our study, Brain utilized an objective measure of medication adherence, the Medication Event Monitoring System (MEMS) (43).

The creators of the DAI-30 found that, among medication-adherent patients with schizophrenia, only 4% were incorrectly classified as non-adherent by their DAI score. Conversely, 17% of noncompliant patients were misidentified as compliant by their scores (8). The authors suggest this discrepancy might be the result of non-adherent patients being less likely to report more negative ATM, which may offer additional insight into our findings (8). Because adherence measures in TMAP were self-reported, it is possible that adherence estimates in our study were inflated or inaccurate. Measured objectively, with the MEMS, non-adherence rates range from 41% to 57% in adult outpatients with schizophrenia (1-4). In our study, only 12% reported poor adherence, suggesting that 88% had a moderate or high level of adherence, which is considerably more than should be expected.

ATM over Time

The majority of studies that have evaluated change in DAI-30 scores in patients with schizophrenia longitudinally found no change in ATM over time, which is consistent with our study findings (8, 50, 51). Conversely, positive changes in ATM over time have been observed in patients taking antipsychotics with close monitoring for adverse events and remission from psychiatric symptoms (52, 67, 68). In TMAP, the use of treatment algorithms for schizophrenia was aimed at improving symptoms and medication management. The majority of subjects (≥70%) reported positive ATM at baseline, which may help to explain the lack of change in mean DAI-30 scores over time in our study.

Limitations

The hypotheses examined in this study were not a priori hypotheses of researchers responsible for the TMAP study design. The study subjects were selected from outpatient community mental health centers in Texas rather than randomly selected from the general population, which may limit the generalizability of study results. The use of self-reported medication adherence assessments is not ideal, but was the most practicable method available. For this study, it is noteworthy that the mental health consumer members of the TMAP research team were adamantly opposed to the use of "pill counts" to assess patient medication adherence. The lag time between assessing changes in ATM (baseline to 6 months) and changes in cognition (baseline to 3 months) may have influenced the lack of significant study findings. Additionally, there was no adjustment for multiple comparisons made when looking at changes in cognition and changes in ATM, which may have influenced findings.

Conclusions

A more complete understanding of factors that influence ATM and adherence can inform strategies for improving overall outcomes in schizophrenia. Consistent with prior studies, we found ATM to be correlated with executive dysfunction (specifically measured via TMT Part B) and negative symptoms (which may themselves be interrelated). It may be that patients with more severe frontal lobe dysfunction and/or negative symptomology are less able to recognize the severity or impact of their illness and appreciate the need for medication. Although antipsychotic medications have not yielded substantive improvements to cognition, adjunctive therapies are being explored. Including measures of

ATM and adherence in those studies could provide further valuable insights.

We found no relationship between adverse events and ATM or between ATM and adherence, perhaps due to sample characteristics (i.e., low adverse event severity and overwhelmingly positive ATM). These results, along with findings from prior literature, raise the question of whether factors that influence ATM act in a linear fashion. It is possible that the relationship between adverse events could be mediated by severity, while the relationship between ATM and adherence may be stronger with more negative ATM. It may be worthwhile for future studies of ATM to consider nonlinear models. Better understanding of factors that influence ATM and treatment adherence in patients with schizophrenia may lead to improvements in quality of life, functionality, and overall outcomes.

Funding

No funding was obtained for this study. The database from the Texas Medication Algorithm Project (TMAP) was used for this study, with permission from the TMAP Research Group.

Conflicts of Interest

Angela Campbell, Julieta Scalo, Jamie Barner, Tami Argo, and Kenneth Lawson report no conflicts of interest related to this manuscript. Alexander Miller has served on two Data Monitoring Committees for studies sponsored by Otsuka Pharmaceutical Group within the past three years. Lynn Crismon has no disclosures to report that are related to this manuscript; however, Lynn Crismon and Alexander Miller were part of the original TMAP research group and TMAP received support from the following sources: National Institute of Mental Health Grant MH-53799, the Robert Wood Johnson Foundation, the Meadows Foundation, the Lightner-Sams Foundation, the Nanny Hogan Boyd Charitable Trust, the Texas Department of Mental Health and Mental Retardation, the Center for Mental Health Services, the Department of Veterans Affairs, a Health Services Research and Development Research Career Scientist Award (RCS92-403), the Betty Jo Hay Distinguished Chair in Mental Health and the Rosewood Corporation Chair in Biomedical Science, the United States Pharmacopeial Convention, Mental Health Connections (a partnership of Dallas County and Texas State mental health authorities with the Department of Psychiatry of the University of Texas Southwestern Medical Center, funded by the Texas State Legislature and the Dallas County Hospital District), The University of Texas at Austin College of Pharmacy, and the Southwestern Drug Corporation Centennial Fellowship in Pharmacy. The following pharmaceutical companies provided unrestricted educational grants: Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Novartis, Organon, Pfizer, and WyethAyerst Laboratories. The authors alone are responsible for the content of this manuscript.

Acknowledgments

We kindly thank the original TMAP research group for allowing us to use the database in order to conduct this research project.

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