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Assessing the Burden of Treatment-Emergent Adverse Events Associated With Atypical Antipsychotic Medications (AAPs) in Schizophrenia: The Patient Perspective

2015 US Psychiatric and Mental Health Congress
September 10–13, 2015
San Diego, CA

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Introduction

- Current treatment guidelines for the treatment of schizophrenia (SCH) suggest that the adverse events (AEs) associated with antipsychotic (AP) drugs are an important consideration in management of the disease.[1-3]
- Clinicians need to individualize and modify AP treatment regimens based on the patient's response to and tolerability of the agents.[1-3]
- Although atypical APs (AAPs; also known as second-generation antipsychotics) are generally associated with a decreased risk of some AEs (eg, extrapyramidal symptoms and tardive dyskinesia) compared with first-generation drugs, they are still associated with a number of AEs, including weight gain and sexual dysfunction.[4,5]
- AEs associated with AAP drugs can be highly burdensome to patients, and negatively affect drug therapy adherence, as well as patients' sense of well-being and quality of life.[4,6]
- Recognition of the importance of incorporating the patient perspective is increasing. For example, the U.S. Food and Drug Administration recognized that patients can and should bring their own evaluation to the benefit-risk profile.[7]
- Further information is needed about the overall tolerability of AAPs, including the occurrence and patient-perceived burden of specific AEs.

Objective

- The objective of this qualitative study was to determine the perceived burden of AEs associated with AAP medications among patients with SCH or schizoaffective disorder and psychiatrists.

Methods

Study Design

- Individual interviews with patients with SCH and a focus group of psychiatrists were conducted.

Study Population

- Patients ≥18 years of age who self-reported a clinician-provided diagnosis of SCH and used ≥1 AAP medication (currently or in the past year) and reported ≥1 AEs associated with an AAP medication
- Practicing psychiatrists who provide and prescribe direct care to adult outpatients with SCH and regularly prescribed ≥1 of the AAP medications to treat these patients

Data Collection

- Information regarding AEs associated with AAPs was collected from patients with SCH during 45-minute individual interviews and from psychiatrists during a 90-minute focus group.
- A semistructured guide and targeted questions were used in both populations to elicit feedback.
- Information collected from patients included
  - Exhaustive list of AEs experienced (via both spontaneous reporting and specific interviewer probes)
  - Frequency of each reported AE
  - Levels of bother for each AE (rank ordered by the individual participants with 1 = most bothersome, 2 = next most bothersome, etc.)
- Information collected from psychiatrists included
  - Exhaustive list of AEs based on personal observations and patient report (by both spontaneous elicitation and specific interviewer probes)
  - Most and least frequently occurring AEs (from their perspectives)
  - Clinically important AEs (rank ordered by each physician with 1 = most clinically important, 2 = next most clinically important, etc.)
  - Levels of patient-perceived bother (from their perspectives) for each clinically important AE (rated by each physician 0 = no bother to 10 = extremely bothered)

Analysis

- Standard qualitative analysis methods were used to identify, characterize, and summarize patterns found in the data collected from the patients and psychiatrists.
- An AE codebook was developed to ensure consistency in organizing and coding the reported AEs. Each reported AE was independently coded by 2 project team members.
- Analysis of the "top 3" rankings was performed using the rankings and scores for the most bothersome AEs (i.e., AEs ranked 1–3 by patients or rated 8–10 by psychiatrists) and ratings for clinical importance (i.e., ranked 1–3 by physicians).
- Descriptive statistics were used as appropriate for the AE codes and rankings/ratings.

Results

Study Population

Patients

- Of the 17 total patients with SCH, 64.7 % (n=11) were male (**Table 1**).

Table 1. Characteristics of Patients With SCH Reported at Screening

Characteristic	Patients N=17 (%)	
Sex, n (%)		
Male	11 (64.7)	
Female	6 (35.3)	
Age, y		
Mean (range)	45.5 (25-59)	
Race/ethnicity,* n (%)		
White	9 (52.9)	
African American	8 (47.1)	
Hispanic/Latino	1 (5.9)	
Mixed race	1 (5.9)	
AAP Medication, n (%)†	**Current**	**Past Year**
Risperidone	4 (23.5)	7 (41.2)
Olanzapine	4 (23.5)	6 (35.3)
Aripiprazole	2 (11.8)	3 (17.6)
Quetiapine	2 (11.8)	2 (11.8)
Lurasidone	2 (11.8)	3 (17.6)
Clozapine	2 (11.8)	3 (17.6)
Ziprasidone	1 (5.9)	3 (17.6)
Paliperidone	1 (5.9)	1 (5.9)
Fluphenazine	1 (5.9)	1 (5.9)
Asenapine	1 (5.9)	0 (0.0)

AAP=atypical antipsychotic; SCH=schizophrenia or schizoaffective disorder.
*Participants could report ≥1 race/ethnicity.
†Because participants could report ≥1 AAP medication, total percentage exceeds 100%. Each generic name may include ≥1 brand name and/or different formulations. Current indicates ongoing at the time of the study, recent indicates having taken within the past year, but not taking at the time of the study.

- The study population consisted of similar proportions of whites (n=9; 52.9%) and African Americans (n=8; 47.1%).
- Risperidone and olanzapine were the most frequent AAPs in current use (23.5% for each).

Psychiatrists

- Psychiatrists (N=4) had a mean of 21.5 years in practice and treated a mean of 301 adults with SCH in the past year.
- The types and use rates of AAPs are listed in **Table 2**.

Table 2. Brief Profile of Psychiatrists Reported at Screening

Characteristic	Psychiatrists (N=4)
Mean years in practice (range)	21.5 (10–35)
AAP medications regularly prescribed,* n (%)	
Quetiapine	4 (100.0)
Aripiprazole	4 (100.0)
Risperidone	4 (100.0)
Olanzapine	4 (100.0)
Lurasidone	4 (100.0)
Ziprasidone	4 (100.0)
Clozapine	3 (75.0)
Paliperidone	3 (75.0)
Asenapine	2 (50.0)
Adult outpatients with SCH treated in past year†	
Mean, (range)	301 (25–1000)
% using AAPs, mean (range)	56.8 (10–80)

AAP=antipsychotic; SCH=schizophrenia or schizoaffective disorder.
*Psychiatrists could report ≥1 AAP medication. Each generic name may include ≥1 brand name and/or different formulations.

Adverse Events

Patients

- Weight changes (n=16; 94.1%), low energy (n=14; 82.4%), and extrapyramidal symptoms (n=13; 76.5%) were the most frequently reported AEs (**Table 3**).
- These AEs were also identified as bothersome by a large proportion of patients with SCH (58.8%–70.6%).
- Weight gain was reported as the most bothersome AE (41.2%).

Psychiatrists

- All 4 psychiatrists selected metabolic syndrome, weight gain, and reduced sexual desire/performance as the top 3 clinically important AEs associated with AAPs (**Table 4**).
- Psychiatrists rated weight gain (100%) and reduced sexual desire/performance, extrapyramidal symptoms, akathisia, and hormonal effects (50% for all) as most bothersome to patients.

Table 3. Most Frequent (>30%), Bothersome, and Most Bothersome AEs Associated With AAPs Reported by Patients With SCH (N=17)

	Patients		
AE	Frequent n (%)	Bothersome n (%)	Most Bothersome n (%)
Weight changes	16 (94.1)	—	—
Weight gain and/or increased appetite	16 (94.1)	12 (70.6)	7 (41.2)
Weight loss and/or decreased appetite	4 (23.5)	0 (0.0)	0 (0.0)
Low energy	14 (82.4)	12 (70.6)	6 (35.3)
Extrapyramidal symptoms	13 (76.5)	10 (58.8)	2 (11.8)
Somnolence/sedation	12 (70.6)	—	—
Need to sleep/excessive sleep/excessive sleepiness	11 (64.7)	6 (35.3)	1 (5.9)
Zombie-like/out of it	4 (23.5)	2 (11.8)	1 (5.9)
Anxiety	11 (64.7)	8 (47.1)	6 (35.3)
Mental anxiety	7 (41.2)	6 (35.3)	6 (35.3)
Physical anxiety	4 (23.5)	4 (23.5)	2 (11.8)
Social anxiety	1 (5.9)	0 (0.0)	1 (5.9)
Cognitive issues	10 (58.8)	6 (35.3)	3 (17.6)
Sexual function	10 (58.8)	—	—
Increased sexual desire/activities	2 (11.8)	1 (5.9)	1 (5.9)
Reduced sexual desire/performance	8 (47.1)	4 (23.5)	2 (11.8)
Increased SCH positive symptoms	8 (47.1)	7 (41.2)	4 (23.5)
Anticholinergic-related dryness	7 (41.2)	—	—
Dry eyes	1 (5.9)	0 (0.0)	0 (0.0)
Dry mouth	6 (35.3)	5 (29.4)	3 (17.6)
Dry skin	0 (0.0)	0 (0.0)	0 (0.0)
Visual problems	7 (41.2)	4 (23.5)	2 (11.8)
Insomnia	6 (35.3)	5 (29.4)	2 (11.8)
Restlessness/akathisia	6 (35.3)	3 (17.6)	3 (17.6)

AAP=atypical antipsychotic; AE=adverse event; SCH=schizophrenia or schizoaffective disorder.

Table 4. AEs Associated With AAPs Reported by Psychiatrists (N=4)

AE	Clinically Important n (%)	Most Clinically Important n (%)	Most Bothersome to Patients n (%)
Metabolic syndrome	4 (100)	4 (100)	N/A*
Weight gain	4 (100)	2 (50.0)	4 (100)
Reduced sexual desire or performance	4 (100)	1 (25.0)	2 (50.0)
Neutropenia	3 (75.0)	3 (75.0)	1 (25.0)
Hyperglycemia	3 (75.0)	2 (50.0)	0 (0.0)
Extrapyramidal symptoms	3 (75.0)	1 (25.0)	2 (50.0)
Hyperlipidemia	3 (75.0)	1 (25.0)	0 (0.0)
Akathisia	3 (75.0)	0 (0.0)	2 (50.0)
QT prolongation	2 (50.0)	2 (50.0)	0 (0.0)
Seizures	2 (50.0)	1 (25.0)	1 (25.0)
Hormonal (eg, galactorrhea, gynecomastia)	2 (50.0)	0 (0.0)	2 (50.0)
Hypotension	2 (50.0)	0 (0.0)	1 (25.0)
Cognitive issues	2 (50.0)	0 (0.0)	1 (25.0)
Diabetes	1 (25.0)	1 (25.0)	1 (25.0)
Hypertension	1 (25.0)	1 (25.0)	0 (0.0)
Low energy	1 (25.0)	0 (0.0)	1 (25.0)
Depressive symptoms	1 (25.0)	0 (0.0)	0 (0.0)
Flat/restricted affect	1 (25.0)	0 (0.0)	0 (0.0)
Somnolence/sedation	1 (25.0)	0 (0.0)	0 (0.0)

AAP=atypical antipsychotic.
*Reported as N/A because it was not specifically mentioned by psychiatrists as bothersome to patients although they did reference other symptoms.

Comparison of Patient and Psychiatrist Results

- **Table 5** compares patients with SCH and psychiatrists on the reported frequency, bother, and clinical importance of AEs associated with AAPs.
- Patients identified frequently occurring AEs, such as weight gain, low energy, somnolence/sedation, cognitive issues, and extrapyramidal symptoms as highly bothersome.
  - Psychiatrists also recognized the AE of weight gain as frequently occurring, clinically important, and highly bothersome to patients.
- Patients rated low energy, somnolence/sedation, and cognitive issues as highly bothersome, whereas these AEs were not rated as highly bothersome by psychiatrists.
- Differences between patients with SCH and psychiatrists were also found for AEs of reduced sexual desire or performance, hormonal effects, and restlessness/akathisia.
  - Psychiatrists identified these AEs as both clinically important and highly bothersome to patients, although these AEs were not rated as highly bothersome by patients.

Table 5. Summary of Frequent, Bothersome, and Clinically Important AEs Associated With AAPs Reported by Patients With SCH and Psychiatrists

	Frequently Occurring†		Highly Bothersome†		Clinically Important§
AEs*	Patients	Psychiatrists	Patients	Psychiatrists	Psychiatrists
Weight gain and/or increased appetite	X	X	X	X	X
Low energy	X	X	X		
Somnolence/sedation	X	X	X		
Cognitive issues	X		X		X
Extrapyramidal symptoms	X		X	X	X
Anxiety	X				
Mental anxiety			X		
Reduced sexual desire or performance		X		X	X
Increased SCH positive symptoms			X		
Hormonal (eg, galactorrhea, gynecomastia)				X	X
Restlessness/akathisia				X	X

AAP=atypical antipsychotic AE=adverse event; SCH=schizophrenia or schizoaffective disorder.
*All AEs listed were reported by at least 1 patient with MDD but did not make the cutoff for most frequently reported, most bothersome, or most clinically important as defined by this table
†By overall frequency of reporting by patients or identified as frequently occurring by psychiatrists.
‡AE reported as bothersome by ≥30% of patients or as most bothersome by ≥20% of patients, and as most bothersome by 2 of the 4 psychatrists.
§Rated only by psychiatrists; AEs identified as clinically important by 2 of 4 psychiatrists.

Conclusions

- **Data from patients with SCH suggest that frequently occurring AEs associated with AAPs are also considered bothersome.**
- **The AE of weight gain was recognized as frequently occurring and bothersome by both patients with SCH and psychiatrists.**
- **Ratings for bother for other AEs suggested a disparity between patients and psychiatrists.**
  - **Cognitive issues, somnolence/sedation, and low energy were reported as very bothersome by patients with SCH.**
  - **Physicians perceived reduced sexual desire or performance, hormonal effects, and restlessness/akathisia to be more bothersome.**
- **Information generated regarding the burden of AEs associated with AAPs can be useful for the development of tools to assess the overall tolerability of these agents.**

Acknowledgments

The data reported on this poster were derived from surveys funded by Lundbeck. The authors retained full independence in the conduct of this research, and received editorial and printing assistance from CHC Group (North Wales, PA), which was supported by Lundbeck LLC.

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