Burden of Adverse Events for Atypical Antipsychotics: an Analysis of the Food and Drug Administration Adverse Event Reporting System

Clement Francois,[1] Ann Hartry,[1] Siddhesh A. Kamat,[2] Mo Dimbil,[3] Keith B. Hoffman[3]

[1]Lundbeck, LLC, Deerfield, IL; [2]Otsuka America Pharmaceutical, Inc., Princeton, NJ; [3]Advera Health Analytics, Inc., Santa Rosa, CA

Background

- In the recent decades, atypical antipsychotics (AAs) have been introduced for the treatment of serious mental illness in an effort to improve efficacy and reduce the side-effect burden of older antipsychotic medications[1,2]
  - Despite the benefit of AAs, there remains a risk of treatment-emergent adverse events (AEs)[3], thereby warranting a need for more tolerable and efficacious treatment options
  - Commonly occurring AEs associated with AAs may be categorized into activating AEs (anxiety, nervousness, akathisia, etc); sedating AEs (somnolence, changes in sleep); and other AEs including cardio-metabolic AEs (changes in weight, diabetes, hypertension)
- The United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database is a voluntary case reporting system that contains information on AEs and medication error reports submitted to the FDA
  - The database supports the FDA's post-marketing safety surveillance program for drugs
  - The informatics structure adheres to the international safety reporting guidance issued by the International Conference on Harmonisation
  - AEs are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology[4]

Study Objective

- This study examined data from FAERS in order to establish the levels and costs of post-marketing, AA-related AEs reported from January 2008 to June 2014

Methods

- FAERS data were collected from January 2008 to June 2014
- AAs available in the US and fourteen common AA-associated AEs were selected for inclusion
  - AAs included aripiprazole, asenapine maleate, clozapine, iloperidone, lurasidone hydrochloride, olanzapine, fluoxetine hydrochloride, paliperidone, quetiapine fumarate, risperidone, ziprasidone
  - All reported primary suspect AEs were recorded and aggregated across the studied drugs
    - "Primary suspect" is a description chosen by the person who submitted the case report as their estimate of the drug most likely to be responsible for the AE
- The Reporting Odds Ratio (ROR) was determined for the AEs
  - ROR is a disproportionality measure commonly used by drug-safety professionals to identify drug-associated AEs that are reported more frequently than expected
  - Elevated RORs indicate a higher than expected reporting rate for a given AE/drug combination
  - RORs were calculated by standard formulas[5] and a ROR ≥2.0 was considered to be an indication of elevated reporting
- Costs per AE were calculated using the RxCost®, which is a proprietary algorithm used for estimating downstream medical costs associated with AE/drug combinations[6]
  - AEs were mapped to MedDRA terms, which were then matched to the corresponding International Classification of Diseases, Ninth Revision, Clinical Modification codes
  - AEs identified as a serious event according to the EudraVigilance list of Important Medical Events (IME)[7] were included in the estimates of total costs of the AEs
  - National hospitalization and aggregate costs for some events not included as serious IMEs were obtained using the Healthcare Cost and Utilization Project (HCUP)[8]

Results

- For this study, 14 specific AEs and groups of AEs were included (**Table 1**)

Table 1. AEs and Groups of AEs Included and Corresponding MedDRA Term Descriptions

AE Terminology Identified in the FDA Database	Corresponding MedDRA Term Description
Activating AEs	
Akathisia	Akathisia
Irregular, jerky movements	Tardive dyskinesia, dyskinesia, muscle contractions involuntary
Continuous muscle spasms and muscle contractions	Dystonia
Restlessness	Restlessness
Agitation	Agitation
Rigid movements or tremors	Parkinsonism, parkinsonian crisis, parkinsonian gait, parkinsonian rest tremor, parkinsonism hyperpyrexia syndrome, parkinson's disease, tremor
Anxiety	Anxiety
Nervousness	Nervousness
Sedating AEs	
Somnolence	Somnolence
Changes in sleep	Terminal insomnia, initial insomnia, insomnia, middle insomnia, behavioural insomnia of childhood, sleep disorder due to general medical condition, insomnia type, insomnia related to another mental condition, sleep disorder, abnormal sleep-related event, somnolence, sudden onset of sleep, sedation
Other AEs	
Glucose or blood sugar abnormalities, diabetes	Diabetes mellitus, diabetes mellitus inadequate control, diabetes mellitus malnutrition-related, insulin-requiring type 2 diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, type 3 diabetes mellitus, insulin resistant diabetes, fulminant type 1 diabetes mellitus, diabetes insipidus, nephrogenic diabetes insipidus, pancreatogenous diabetes, increased insulin requirement, latent autoimmune diabetes in adults, diabetes with hyperosmolarity, cystic fibrosis related diabetes, hyperglycemia, blood glucose increased, blood glucose abnormal, glycosylated hemoglobin increased, glycosylated hemoglobin
Changes in weight	Obesity, overweight, central obesity, weight fluctuation, abnormal weight gain, weight increased, weight abnormal, binge eating, eating disorder, eating disorder symptom, food craving, body fat disorder, fat tissue increased, increased appetite
Trouble with digestive system	Nausea, vomiting, vomiting projectile, vomiting psychogenic, retching, procedural nausea, procedural vomiting, prophylaxis of nausea and vomiting, dyspepsia, dry mouth
Trouble with bowel system	Constipation, diarrhea

- **Table 2** illustrates disproportional reporting rates of the AEs analyzed by ROR
  - Disproportionally elevated reporting was observed for activating AEs of agitation, akathisia, restlessness, continuous muscle spasms or contractions, rigid movements or tremors, and jerky movements; sedating AEs of somnolence and sleep changes; and other AEs of weight changes and glucose abnormalities
  - In contrast, anxiety, nervousness, digestive trouble, and bowel trouble did not appear to have class-wide elevations in reporting

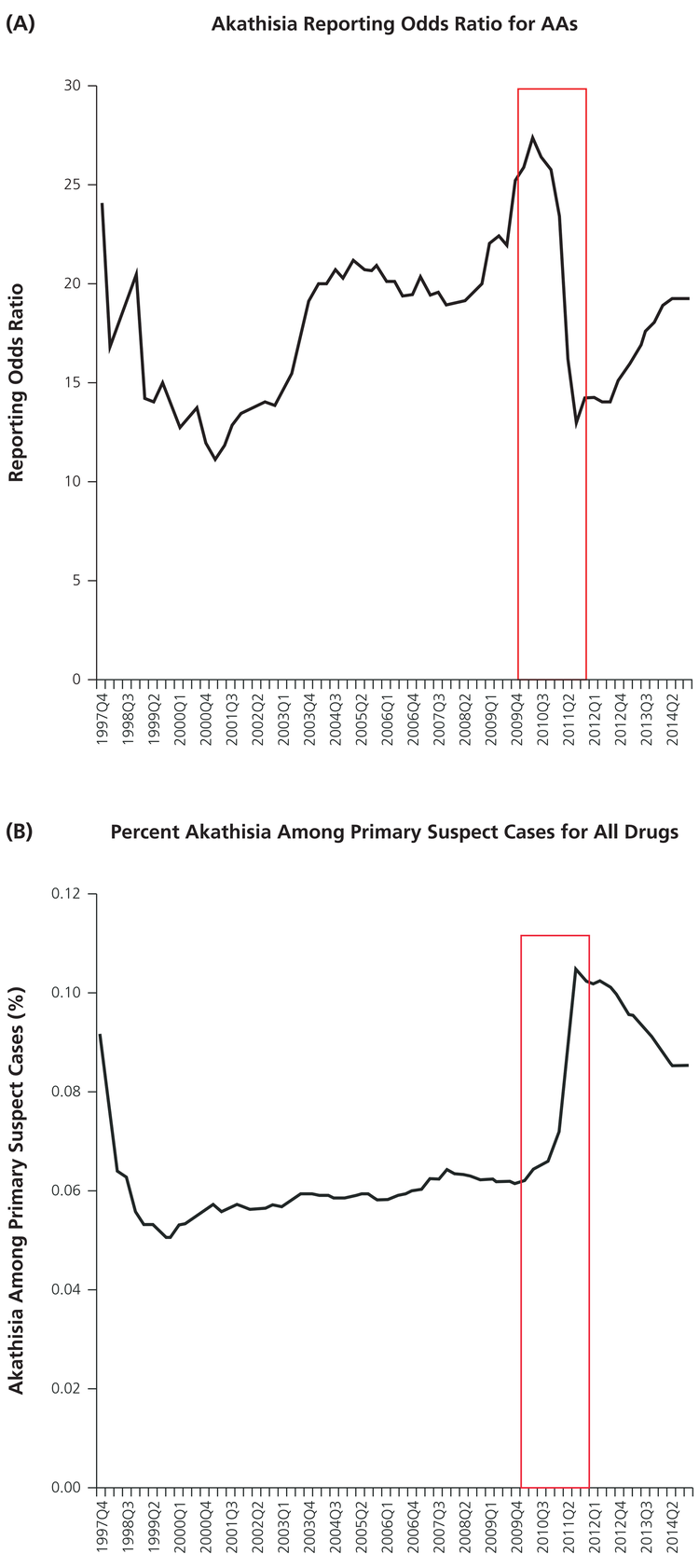
Table 2. Cumulative Disproportional Reporting Rate for AEs for a Combined Class of Antipsychotics

AE	Primary Suspect Cases	ROR (95% CI) [ROR ≥2.0 indicates elevated reporting]
Activating AEs		
Akathisia	1,948	19.32 (18.27–20.42)
Irregular, jerky movements	5,475	6.04 (5.86–6.21)
Continuous muscle spasms and muscle contractions	1,794	5.94 (5.65–6.25)
Restlessness	1,643	4.50 (4.27–4.74)
Agitation	3,453	3.74 (3.61–3.87)
Rigid movements or tremors	4,958	2.57 (2.49–2.64)
Anxiety	3,601	1.24 (1.20–1.28)
Nervousness	739	1.03 (0.95–1.11)
Sedating AEs		
Somnolence	4,607	2.99 (2.90–3.08)
Changes in sleep	13,173	2.74 (2.69–2.79)
Other AEs		
Glucose or blood sugar abnormalities, diabetes	18,518	5.96 (5.86–6.05)
Changes in weight	10,917	5.22 (5.11–5.33)
Trouble with digestive system	6,164	0.53 (0.52–0.55)
Trouble with bowel system	3,243	0.53 (0.51–0.55)

CI, confidence interval.

- To visualize evolution of AA ROR over time, ROR for akathisia is illustrated in **Figure 1A** from the time of the start of database collection until the end of the study period (1998–2014)
  - To investigate the apparent decrease in ROR from the period of 2009 to 2011, percent akathisia was determined for primary suspect cases for all drugs in the database, not just AAs (**Figure 1B**)
  - The apparent decrease was shown to be a result of the total increase of akathisia during that time period (see red box in **Figure 1A and 1B**)

Figure 1. Evolution of Akathisia Reporting Odds Ratio for AAs (A) and All Drugs in the Database (B)



- Using RxCost®, the total costs from the period of 2008 to 2012 for the serious AEs (per IME) recorded in the FAERS database were estimated at over 356 million $USD (**Table 3**)

Table 3. Estimated Annual and Total Costs of AEs, 2008–2012

Year	2008	2009	2010	2011	2012
Annual cost of AEs, $USD	41,115,271	77,262,470	67,999,391	101,177,983	68,656,665
Total estimated costs from 2008 to 2012, $USD	356,211,780				

- HCUP data were available to derive costs for a subset of the AEs specified for the ROR study (**Table 4**)

Table 4. Mean 2015 Cost Estimate for a Subset of AEs

AE	Mean Cost,* $USD
Activating AEs	
Continuous muscle spasms and muscle contractions	20,388
Rigid movements or tremors	11,095
Irregular, jerky movements	6,249
Akathisia	6,248
Anxiety	4,725
Sedating AEs	
Changes in sleep	4,888
Other AEs	
Trouble with digestive system	5,197

*Note: Cost estimates are for 2015 costs per AE were calculated using the RxCost® (described in Methods).

Limitations

- The FAERS reporting system does not require that a causal relationship between a product and an event be proven and, therefore, there is no certainty that the reported event was actually due to the product
- The AEs reported may not be a complete list of AEs as certain factors, such as the market time of a product or publicity regarding an event, can influence whether or not an event will be reported
- Some of the AEs presented may be associated with patients' preexisting diseases, disorders, or predispositions and may not be directly caused by the administered drug
- Post-marketing data may be subjected to biases, such as underreporting and stimulated reporting, or may be confounded by comorbidities, and, as such, may not represent all AEs caused by a drug

Conclusions

- Activation-, sedation-, and weight gain-related AEs continue to persist, thereby warranting a need for additional tolerable and efficacious treatment alternatives
- While AAs were expected to have a reduced side-effect burden compared with older antipsychotics, patients still report higher than expected AE rates
- These AEs may have costly implications for both patients and payers

References

1. Volavka J, et al. *Expert Opin Pharmacother*. 2009;10(12):1917-28.
2. Leucht S, et al. *Lancet*. 2013;382(9896):951-62.
3. Cha DS, et al. *Expert Opin Pharmacother*. 2012;13(11):1587-98.
4. MedDRA. Medical Dictionary for Regulatory Activities and the Maintenance and Support Services. http://www.meddra.org. Accessed September 25, 2015.
5. Bate A, et al. *Pharmacoepidemiology and Drug Safety*. 2009;18(6):427-36.
6. RxCost® whitepaper. http://info.adverahealth.com/whitepaper-rxcost. Accessed September 25, 2015.
7. Important Medical Event Terms. https://eudravigilance.ema.europa.eu/human/textforIME.asp. Accessed September 23, 2015.
8. HCUP. Healthcare Cost and Utilization Project. http://hcupnet.ahrq.gov/HCUPnet.jsp. Accessed September 21, 2015.

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Declaration of Financial/Other Relationship

Clement Francois and Ann Hartry are employees of Lundbeck, LLC. Siddhesh A. Kamat is an employee of Otsuka America Pharmaceutical, Inc. Mo Dimbil and Keith B. Hoffman are employees of Advera Health Analytics, which received funding from Otsuka America Pharmaceutical, Inc., and Lundbeck, LLC in connection with the conduction of this study.

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