Differences in Antipsychotic-Related Adverse Events in Adult, Pediatric, and Geriatric Populations

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Abstract

In recent years, antipsychotic medications have increasingly been used in pediatric and geriatric populations, despite the fact that many of these drugs were approved based on clinical trials in adult patients only. Preliminary studies have shown that the "off-label" use of these drugs in pediatric and geriatric populations may result in adverse events not found in adults. In this study, we utilized the large-scale U.S. Food and Drug Administration (FDA) Adverse Events Reporting System (AERS) database to look at differences in adverse events from antipsychotics among adult, pediatric, and geriatric populations. We performed a systematic analysis of the FDA AERS database using MySQL by standardizing the database using structured terminologies and ontologies. We compared adverse event profiles of atypical versus typical antipsychotic medications among adult (18-65), pediatric (age < 18), and geriatric (> 65) populations. We found statistically significant differences between the number of adverse events in the pediatric versus adult populations with aripiprazole, clozapine, fluphenazine, haloperidol, olanzapine, quetiapine, risperidone, and thiothixene, and between the geriatric versus adult populations with aripiprazole, chlorpromazine, clozapine, fluphenazine, haloperidol, paliperidone, promazine, risperidone, thiothixene, and ziprasidone (p < 0.05, with adjustment for multiple comparisons). Furthermore, the particular types of adverse events reported also varied significantly between each population for aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone (Chi-square, p < 10^-6). Diabetes was the most commonly reported side effect in the adult population, compared to behavioral problems in the pediatric population and neurologic symptoms in the geriatric population. We also found discrepancies between the frequencies of reports in AERS and in the literature. Our analysis of the FDA AERS database shows that there are significant differences in the numbers and types of adverse events among these age groups and between atypical and typical antipsychotics. It is important for clinicians to be mindful of these differences when prescribing antipsychotics, especially when prescribing medications off-label.

Introduction

While antipsychotic medications were initially approved based on clinical trials in adult populations, they are commonly prescribed "off-label" in pediatric and geriatric populations [1-2]. In addition, they are increasingly being prescribed to children. Between the 1993 - 1998 and 2005 - 2009 time periods, visits including a prescription for antipsychotics per 100 people increased from 0.24 to 1.83 for children, 0.78 to 3.76 for adolescents, and 3.25 to 6.18 for adults; moreover, antipsychotics were included in 31.1% of youth visits to psychiatrists [3]. While antipsychotics are among the most effective drugs for the treatment of schizophrenia, mania, or acute psychotic reactions, these medications are often prescribed to children and adolescents for non-FDA approved indications, such as disruptive behaviors and aggression [4-5]. Similarly, antipsychotics are frequently used in the elderly and are prescribed to more than a quarter of Medicare patients in nursing homes, with common conditions including dementia, delirium, and behavioral disturbances [2]. However, the use of these medications may result in unexpected adverse events that are specific to the pediatric and geriatric populations [6]. In our study, we sought to elucidate the differences in adverse events between pediatric, adult, and geriatric populations using the FDA's Adverse Events Reporting System (AERS), a database that has collected information about adverse events since 1998 [7]. AERS is the FDA's primary tool for post-marketing adverse event surveillance, with over 250,000 adverse event reports annually [8]. A key strength of the AERS database is the ability to analyze a massive dataset and discover potentially new information regarding drug-related adverse events warranting further investigation. For instance, a recent paper probing the AERS database and found a potential link between amisulpride, cyamemazine, and olanzapine and torsadogenic risk [9]. Drug manufacturers are required to submit adverse event reports, while healthcare providers can voluntarily submit information.
Materials And Methods

We initially imported AERS quarterly data from January 2004 to September 2008 into the MySQL program (v.1.2.17) (Oracle Corp., Redwood Shores, CA). A table was created that mapped all the various drug names for antipsychotics to a generic name and a drug class (typical vs. atypical) using RxNorm (U.S. National Library of Medicine, Bethesda, MD) and Micromedex® (Truven Health Analytics, Greenwood Village, CO) (Table 1). Next, we joined this table with the AERS drug table (matching by DRUGNAME), the AERS demo table (matching by ISR, which stands for individual safety report), and the AERS REAC table (also matching by ISR). We first retrieved the total number of adverse events associated with each drug name, generic name, and drug class. Next, we created a yearage variable (which standardized all ages in AERS to be reported in years using the AGE and AGE_COD variables) as well as the GNDR_COD variable (which was reported as either “M” or “F”) in order to repeat this analysis on the following five subgroups: yearage < 18 (pediatrics), 18 ≥ yearage ≤ 65 (adults), and yearage > 65 (geriatrics), GNDR_COD = “M” (males), and GNDR_COD = “F” (females).

| Drug Name | Generic Name | Drug Class |
|-----------|--------------|------------|
| Abilify   | Aripiprazole | Atypicals  |
| Aripiprazole | Aripiprazole | Atypicals  |
| Chlorpromazine | Chlorpromazine | Typical |
| Clozapine | Clozapine | Atypicals  |
| Clozaril | Clozapine | Atypicals  |
| Decazate | Fluphenazine | Typical |
| Dozine  | Chlorpromazine | Typical |
| Fazalco | Clozapine | Atypicals  |
| Fentazin | Perphenazine | Typical |
| Fluphenazine | Fluphenazine | Typical |
| Fortunant | Haloperidol | Typical |
| Geodon | Ziprasidone | Atypicals  |
| Haldol   | Haloperidol | Typical |
| Haloperidol | Haloperidol | Typical |
| Invega   | Paliperidone | Atypicals  |
| Kentace  | Haloperidol | Typical |
| Largactil | Chlorpromazine | Typical |
| Loxapac  | Loxapine | Typical |
| Loxapine | Loxapine | Typical |
| Loxitane | Loxapine | Typical |
| Mellaril | Thioridazine | Typical |
| Mesoridazine | Mesoridazine | Typical |
| Moban    | Molindone | Typical |
| Moditen  | Fluphenazine | Typical |
| Navane   | Thiothixene | Typical |
| Noxene   | Thiothixene | Typical |
| Olanzapine | Olanzapine | Atypicals  |
| Orap     | Pimozide | Typical |
| Ormazine | Chlorpromazine | Typical |
| Permitil | Fluphenazine | Typical |
Next, for each drug, we computed the percent of antipsychotic-related adverse events that the drug represented in each population. We then used the z-test of proportions to compare this percent for each drug in the following categories: pediatrics vs. adults, adults vs. geriatrics, and males vs. females. This process was conducted separately for typical and atypical drugs. This resulted in a z-score and a p-value for each comparison, which was then adjusted using a Bonferroni correction for multiple comparisons, making the significance threshold $0.05/26 = 1.92 \times 10^{-3}$.

Afterward, we retrieved the count of each individual adverse event associated with each generic drug, ordered by the frequency of occurrence in each population. We made sure not to include irrelevant or vague side effects in our top results, excluding terms such as "DRUG INTERACTION," "ACCIDENTAL EXPOSURE," and "ACCIDENTAL DRUG INTAKE BY CHILD." In order to compare the frequencies of the different adverse events in the adult, pediatric, and geriatric populations, we conducted a Chi-square test. For each drug, we selected the top five adverse events in adults and added a sixth column that contained the sum of all other adverse events. We chose the top five since this minimized the number of cells in the Chi-square calculation that contained an expected value less than 5, which is not ideal for the Chi-square test. Next, we compared the frequency of these particular adverse events in the adult, pediatric, and geriatric populations using a 3 by 6 Chi-square table with 10 degrees of freedom, and we calculated p-values for each of seven major drugs—aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone—using the R statistical program (v2.12.2). We also used the MedRDA (Medical Directory for Regulatory Activities: International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland) hierarchy to map MedDRA Preferred Terms (the default FDA coding) to high-level terms and determined the frequency of the high-level terms in the three populations.

**TABLE 1: List of Antipsychotic Medications Mapped to Generic Name and Drug Class**

| Drug          | Generic Name     | Drug Class     |
|---------------|------------------|----------------|
| Perphenazine  | Perphenazine     | Typicals       |
| Pimozide      | Pimozide         | Typical        |
| Primazine     | Promazine        | Typical        |
| Prolixin      | Fluphenazine     | Typical        |
| Promazine     | Promazine        | Typical        |
| Quetiapine    | Quetiapine       | Atypicals      |
| Rideril       | Thoridazine      | Typical        |
| Risperdal     | Risperidone      | Atypicals      |
| Risperidone   | Risperidone      | Atypicals      |
| Serenace      | Haloperidol      | Typical        |
| Seroquel      | Quetiapine       | Atypicals      |
| Spanine       | Promazine        | Typical        |
| Stelazine     | Trifluoperazine  | Typical        |
| Symbyax       | Olanzapine       | Atypicals      |
| Thoridazine   | Thoridazine      | Typical        |
| Thiothixene   | Thiothixene      | Typical        |
| Thorazine     | Chlorpromazine   | Typical        |
| Trifluoperazine| Trifluoperazine  | Typical        |
| Trilafon      | Promazine        | Typical        |
| Vesprin       | Triflupromazine  | Typical        |
| Ziprasidone   | Ziprasidone      | Atypicals      |
| Zyprexa       | Olanzapine       | Atypicals      |
Next, we took the list of the top five adverse events for the seven drugs in the three populations and used Medical Subject Headings (MeSH terms) to evaluate how many times a particular drug-adverse event combination was indexed in PubMed for the three populations. For instance, for the side-effect “TREMOR” for aripiprazole in the geriatric population, we would have used the following search term: ‘aripiprazole’ [Substance Name] AND (‘Aged’[Mesh]) AND tremor. We then compared the number of reports in AERS and in the literature. For the drug, population, and adverse event combinations that had fewer than five reports in the literature, we manually examined the results to ensure their validity and highlighted the ones that we confirmed to have less than five reports.

Results
A summary of the populations we studied is shown in Table 2.

| Category                              | Value  |
|---------------------------------------|--------|
| Total number of patients              | 61,380 |
| Mean age ± SD                         | 45.7 ± 20.0|
| Patients where age < 18               | 3,578  |
| Patients where age ≥ 18 and age ≤ 65  | 32,660 |
| Patients where age > 65               | 7,260  |
| Patients where age is not available   | 17,882 |
| Male patients                         | 27,783 |
| Female patients                       | 29,780 |
| Gender NA (null, unknown, or not specified) | 3,817 |

TABLE 2: Demographics: Summary of the Population

The percentage of antipsychotic-related side effects was often significantly different in the pediatric, adult, and geriatric populations for atypical and typical antipsychotics as shown in Tables 3-4.

| Generic Name | % of Adverse Events | p-value (vs. Adults) | Statistical Significance |
|--------------|---------------------|----------------------|-------------------------|
|              | Pediatrics | Adults | Geriatrics | Pediatrics | Geriatrics |          |
| Aripiprazole | 25.9       | 9.8    | 4.8        | 0          | 0          | Both      |
| Clozapine    | 4.6        | 17.3   | 13.9       | 0          | 2.7e-14   | Both      |
| Olanzapine   | 16.1       | 26.0   | 25.6       | 0          | 0.23       | Pediatrics|
| Paliperidone | 0.6        | 0.6    | 0.2        | 0.43       | 3.5e-5     | Geriatrics|
| Quetiapine   | 24.4       | 27.2   | 26.1       | 2.6e-9     | 0.019      | Pediatrics|
| Risperidone  | 23.3       | 14.4   | 27.5       | 0          | 0          | Both      |
| Ziprasidone  | 5.1        | 4.6    | 1.9        | 0.077      | 0          | Geriatrics|
| TOTALS       | 100.0      | 100.0  | 100.0      |            |            |           |

TABLE 3: Comparison of the Number of Adverse Events in Each Population for Atypical Antipsychotics

Results were statistically significant either for pediatrics vs. adults, geriatrics vs. adults, or both. The significance threshold was 0.05/26 = 1.92 x 10^-3. The p-values that R found to be extremely low are labeled as "0." Items that were statistically significant are in bold.
| Generic Name | % of Adverse Events | p-value (vs. Adults) | Statistical Significance |
|--------------|---------------------|----------------------|-------------------------|
|              | Pediatrics | Adults | Geriatrics | Pediatrics | Geriatrics |               |
| Chlorpromazine | 20.3 | 17.1 | 12.1 | 0.066 | 3.31e-6 | Geriatrics |
| Fluphenazine | 0.3 | 5.1 | 2.4 | 4.3e-5 | 4.39e-6 | Both |
| Haloperidol | 64.9 | 56.3 | 72.8 | 0.0011 | 0 | Both |
| Loxapine | 2.8 | 2.7 | 1.9 | 0.46 | 0.043 | -- |
| Molindone | 0.0 | 0.2 | 0.1 | 0.20 | 0.27 | -- |
| Perphenazine | 0.3 | 2.7 | 2.3 | 0.0038 | 0.19 | -- |
| Pimozide | 3.4 | 1.6 | 1.3 | 0.0082 | 0.17 | -- |
| Promazine | 0.6 | 2.8 | 0.1 | 0.0095 | 9.39e-10 | Geriatrics |
| Thioridazine | 5.5 | 3.9 | 3.4 | 0.070 | 0.20 | -- |
| Thiothixene | 0.0 | 4.5 | 0.9 | 4.9e-5 | 1.24e-10 | Both |
| Trifluoperazine | 0.9 | 2.9 | 2.0 | 0.017 | 0.031 | -- |
| TOTALS | 100.0 | 100.0 | 100.0 | | | |

**TABLE 4: Comparison of the Number of Adverse Events in Each Population for Typical Antipsychotics**

Results were statistically significant either for pediatrics vs. adults, geriatrics vs. adults, or both. The significance threshold was 0.05/26 = 1.92 x 10^{-3}. The p-values that R found to be extremely low are labeled as "0." Items that were statistically significant are in bold.

Eight antipsychotics were associated with a significant difference in the number of adverse events in the pediatric vs. adult populations, including aripiprazole, clozapine, fluphenazine, haloperidol, olanzapine, quetiapine, risperidone, and thiothixene. Ten antipsychotics were associated with a significant difference in the number of adverse events in the adult vs. geriatric populations, including aripiprazole, chlorpromazine, clozapine, fluphenazine, haloperidol, paliperidone, promazine, risperidone, thiothixene, and ziprasidone.

When we compared the distributions of adverse events in the adult population to the pediatric and geriatric populations, Chi-square tests revealed that they were significantly different, as the p-values were 4.33e-32, 1.68e-32, 2.60e-35, 6.96e-106, 4.50e-124, 3.45e-65, and 1.35e-7, respectively, for aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone. Tables comparing the number of reports in the literature to those in the AERS database for the top five adverse events in seven major antipsychotics revealed some outliers in the three populations, as evidenced by the reports with less than five cases in the literature (Tables 5-6).
### TABLE 5: Top Adverse Events in the Pediatric Population

The searches that have five or less PubMed articles are in bold.

| Generic Name | Event | Geriatrics |
|--------------|-------|------------|
| Clozapine    | SOMNOLENCE | 31         |
| Clozapine    | WHITE BLOOD CELL COUNT DECREASED | 26         |
| Clozapine    | SEDATION | 21         |
| Clozapine    | OTHERS | 1,069       |
| Haloperidol  | SOMNOLENCE | 35         |
| Haloperidol  | TREMOR | 23         |
| Haloperidol  | EXTRAPYRAMIDAL DISORDER | 18         |
| Haloperidol  | MUSCLE SPASMS | 15         |
| Haloperidol  | NEUROLEPTIC MALIGNANT SYNDROME | 14         |
| Haloperidol  | OTHERS | 770         |
| Olanzapine   | WEIGHT INCREASED | 106        |
| Olanzapine   | AGGRESSION | 69         |
| Olanzapine   | SUICIDAL IDEATION | 58         |
| Olanzapine   | ABNORMAL BEHAVIOUR | 46         |
| Olanzapine   | COMPLETED SUICIDE | 44         |
| Olanzapine   | OTHERS | 3,755       |
| Quetiapine   | WEIGHT INCREASED | 121        |
| Quetiapine   | SUICIDAL IDEATION | 80         |
| Quetiapine   | TACHYCARDIA | 74         |
| Quetiapine   | CONVULSION | 72         |
| Quetiapine   | AGGRESSION | 70         |
| Quetiapine   | OTHERS | 4,745       |
| Risperidone  | AGGRESSION | 112        |
| Risperidone  | WEIGHT INCREASED | 69         |
| Risperidone  | CONVULSION | 66         |
| Risperidone  | SUICIDAL IDEATION | 65         |
| Risperidone  | ABNORMAL BEHAVIOUR | 54         |
| Risperidone  | OTHERS | 4,015       |
| Ziprasidone  | DYSTONIA | 26         |
| Ziprasidone  | SUICIDAL IDEATION | 25         |
| Ziprasidone  | DEPRESSION | 20         |
| Ziprasidone  | SUICIDE ATTEMPT | 20         |
| Ziprasidone  | WEIGHT INCREASED | 19         |
| Ziprasidone  | OTHERS | 943         |
| Medication    | Adverse Event                  | Count |
|--------------|--------------------------------|-------|
| Aripiprazole | Tremor                         | 27    |
| Aripiprazole | Neuroleptic Malignant Syndrome | 22    |
| Aripiprazole | Parkinsonism                   | 21    |
| Aripiprazole | Death                          | 18    |
| Aripiprazole | Gait Disturbance               | 15    |
| Aripiprazole | Others                         | 1,087 |
| Clozapine    | Death                          | 174   |
| Clozapine    | Pneumonia                      | 100   |
| Clozapine    | Pyrexia                        | 63    |
| Clozapine    | Somnolence                     | 50    |
| Clozapine    | Fall                           | 46    |
| Clozapine    | Others                         | 3,117 |
| Haloperidol  | Agitation                      | 78    |
| Haloperidol  | Confusional State              | 75    |
| Haloperidol  | Fall                           | 68    |
| Haloperidol  | Pyrexia                        | 67    |
| Haloperidol  | Delirium                       | 62    |
| Haloperidol  | Others                         | 5,196 |
| Olanzapine   | Fall                           | 175   |
| Olanzapine   | Confusional State              | 142   |
| Olanzapine   | Diabetes Mellitus              | 138   |
| Olanzapine   | Cerebrovascular Accident       | 107   |
| Olanzapine   | Pneumonia                      | 100   |
| Olanzapine   | Others                         | 9,494 |
| Quetiapine   | Fall                           | 155   |
| Quetiapine   | Death                          | 111   |
| Quetiapine   | Confusional State              | 107   |
| Quetiapine   | Agitation                      | 103   |
| Quetiapine   | Pneumonia                      | 91    |
| Quetiapine   | Others                         | 7,377 |
| Risperidone  | Somnolence                     | 161   |
| Risperidone  | Death                          | 159   |
| Risperidone  | Confusional State              | 152   |
| Risperidone  | Fall                           | 135   |
| Risperidone  | Asthenia                       | 117   |
| Risperidone  | Others                         | 8,770 |
| Ziprasidone  | Myocardial Infarction          | 15    |
| Ziprasidone  | Coma                           | 15    |
| Ziprasidone  | Loss of Consciousness          | 11    |
Chi-square analysis was performed to compare the actual distribution of adverse events between the different populations for each drug. Seven commonly prescribed antipsychotics are presented in Table 7: aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone.

### TABLE 6: Top Adverse Events in the Geriatric Population

The searches that have five or less PubMed articles are in bold.
The distribution of antipsychotic-related adverse events was compared between the pediatric, adult, and geriatric populations for seven major antipsychotics. For each major antipsychotic drug, adverse events were ordered by their frequency in the adult population, the top five were selected (and the rest designated as "other"), and their distribution was compared using the Chi-square test. The resultant p-value is in the final column.

The top five adverse events for less common drugs are listed in Table 8.
| Medication      | Effect                               | Count  | Associated Effect                        | Count  |
|-----------------|--------------------------------------|--------|-----------------------------------------|--------|
| Loxapine        | Pregnancy                            | 2      | Lactic Acidosis                         | 10     |
| Loxapine        | Renal Cyst                           | 2      | Blood Creatine Phosphokinase Increased  | 9      |
| Loxapine        |                                        |        | Anaemia                                 | 3      |
| Mesoridazine    |                                        | 0      | Aggression                              | 4      |
| Mesoridazine    |                                        | 0      | Excessive Masturbation                   | 3      |
| Mesoridazine    |                                        | 0      | Rash Papular                            | 3      |
| Mesoridazine    |                                        | 0      | Skin Ulcer                              | 3      |
| Mesoridazine    |                                        | 0      | Rash                                    | 2      |
| Molindone       | Neuroleptic Malignant Syndrome        | 2      | Prescribed Overdose                      | 3      |
| Molindone       | Myositis                             | 1      | Convulsions                             | 3      |
| Molindone       | Pyrexia                              | 1      | Diabetes Mellitus Non-Insulin-Dependent  | 2      |
| Molindone       | Viral Myositis                       | 1      | Anger                                   | 2      |
| Molindone       | Rash                                 | 1      | Abdominal Distension                    | 2      |
| Paliperidone    | Neuroleptic Malignant Syndrome       | 10     | Galactorrhoea                           | 30     |
| Paliperidone    | Headache                             | 9      | Extrapyrimal Disorder                   | 23     |
| Paliperidone    | Confusional State                    | 8      | Akathisia                               | 17     |
| Paliperidone    | Palpitations                         | 8      | Oedema Peripheral                       | 17     |
| Paliperidone    | Dystonia                             | 6      | Dystonia                                | 12     |
| Perphenazine    |                                      | 0      | Vomiting                                | 11     |
| Perphenazine    |                                      | 0      | Completed Suicide                       | 10     |
| Perphenazine    |                                      | 0      | Diabetes Mellitus                       | 10     |
| Perphenazine    |                                      | 0      | Drug Interaction                        | 8      |
| Perphenazine    |                                      | 0      | Drug Ineffective                        | 8      |
| Pimozide        | Weight Increased                     | 4      | Cardiac Arrest                          | 12     |
| Pimozide        | Diarrhoea                            | 4      | Suicide Attempt                         | 8      |
| Pimozide        | Rectal Haemorrhage                   | 4      | Drug Interaction                        | 7      |
| Pimozide        | Somnolence                           | 3      | Overdose                                | 6      |
| Pimozide        | Alopexia                              | 2      | Anxiety                                 | 6      |
| Promazine       | Neonatal Diabetes Mellitus           | 1      | Diabetes Mellitus                       | 33     |
| Promazine       | Premature Baby                       | 1      | Pancreatitis                            | 15     |
| Promazine       | Death                                 | 1      | Myocardial Infarction                   | 15     |
| Promazine       | Diaphragmatic Hernia                 | 1      | Blood Pressure Decreased                | 14     |
| Promazine       | Pulmonary Hypoplasia                 | 1      | Myocarditis                             | 14     |
| Thoridazine     | Nausea                               | 8      | Headache                                | 32     |
| Thoridazine     | Alopexia                              | 8      | Dizziness                               | 29     |
| Thoridazine     | Vomiting                             | 5      | Depression                              | 25     |
| Thoridazine     | Acholia                              | 5      | Anxiety                                 | 24     |
| Generic    | Event Pediatrics                        | N   | Event Adults                       | N   | Event Geriatrics | N   |
|------------|----------------------------------------|-----|------------------------------------|-----|------------------|-----|
| Aripiprazole | Neurological signs and symptoms NEC    | 196 | Neurological signs and symptoms NEC | 577 | Neurological signs and symptoms NEC | 56  |
| Aripiprazole | Dyskinesias and movement disorders NEC | 172 | Dyskinesias and movement disorders NEC | 445 | General signs and symptoms NEC | 36  |
| Aripiprazole | Disturbances in consciousness NEC      | 143 | Anxiety symptoms                   | 420 | Muscle tone abnormal     | 33  |
| Aripiprazole | Physical examination procedures        | 133 | General signs and symptoms NEC     | 408 | Dyskinesias and movement disorders NEC | 33  |
| Aripiprazole | General signs and symptoms NEC         | 117 | Physical examination procedures    | 402 | Parkinson’s disease and parkinsonism | 29  |
| Clozapine  | Disturbances in consciousness NEC      | 78  | White blood cell analyses          | 1,222 | General signs and symptoms NEC | 193 |
| Clozapine  | White blood cell analyses              | 56  | Neutropenias                       | 1,137 | Death and sudden death     | 192 |
| Clozapine  | Neutropenias                           | 52  | Disturbances in consciousness NEC  | 952  | Disturbances in consciousness NEC | 145 |
| Clozapine  | Rate and rhythm disorders NEC          | 42  | General signs and symptoms NEC     | 887  | Lower respiratory tract and lung infections | 121 |
| Clozapine  | Neurological signs and symptoms NEC    | 39  | Neurological signs and symptoms NEC | 831  | Lower respiratory tract infections NEC | 117 |
| Haloperidol | Disturbances in consciousness NEC      | 51  | Disturbances in consciousness NEC  | 471  | Neurological signs and symptoms NEC | 246 |
| Haloperidol | Medication errors due to accidental exposures | 50  | Neurological signs and symptoms NEC | 425  | Disturbances in consciousness NEC | 162 |
| Haloperidol | Muscle tone abnormal                   | 39  | General signs and symptoms NEC     | 381  | General signs and symptoms NEC | 141 |

The top five adverse events for the seven major antipsychotics mapped to MedDRA high-level terms are listed in Table 9.
| Drug         | Event Description                                      | Number | MedDRA® High-Level Terms                       | Number |
|--------------|--------------------------------------------------------|--------|-----------------------------------------------|--------|
| Haloperidol  | Dyssomnias                                             | 35     | Breathing abnormalities                       | 278    |
| Haloperidol  | Dyskinesias and movement disorders NEC                 | 33     | Liver function analyses                       | 274    |
| Olanzapine   | Suicidal and self-injurious behavior                   | 198    | Diabetes mellitus (incl subtypes)             | 2,403  |
| Olanzapine   | Physical examination procedures                        | 150    | Physical examination procedures               | 2,016  |
| Olanzapine   | Neurological signs and symptoms NEC                    | 134    | General signs and symptoms NEC                | 1,556  |
| Olanzapine   | Behavior and socialization disturbances                | 130    | Disturbances in consciousness NEC             | 1,551  |
| Olanzapine   | General signs and symptoms NEC                         | 126    | Non-site specific injuries NEC                | 201    |
| Quetiapine   | Suicidal and self-injurious behavior                   | 235    | Diabetes mellitus (incl subtypes)             | 2,432  |
| Quetiapine   | Neurological signs and symptoms NEC                    | 205    | General signs and symptoms NEC                | 1,531  |
| Quetiapine   | Physical examination procedures                        | 178    | Neurological signs and symptoms NEC           | 1,514  |
| Quetiapine   | General signs and symptoms NEC                         | 172    | General signs and symptoms NEC                | 221    |
| Quetiapine   | Disturbances in consciousness NEC                      | 170    | Disturbances in consciousness NEC             | 1,386  |
| Quetiapine   | Neurological signs and symptoms NEC                    | 205    | Non-site specific injuries NEC                | 181    |
| Risperidone  | Behavior and socialization disturbances                | 217    | General signs and symptoms NEC                | 966    |
| Risperidone  | Suicidal and self-injurious behavior                   | 202    | Disturbances in consciousness NEC             | 870    |
| Risperidone  | Neurological signs and symptoms NEC                    | 194    | Neurological signs and symptoms NEC           | 867    |
| Risperidone  | General signs and symptoms NEC                         | 128    | Asthenic conditions                           | 245    |
| Risperidone  | Neurological signs and symptoms NEC                    | 194    | General signs and symptoms NEC                | 223    |
| Ziprasidone  | Behavior and socialization disturbances                | 52     | Anxiety symptoms                              | 283    |
| Ziprasidone  | Neurological signs and symptoms NEC                    | 47     | Diabetes mellitus (incl subtypes)             | 281    |
| Ziprasidone  | Anxiety symptoms                                       | 41     | Disturbances in consciousness NEC             | 280    |

| Drug         | Event Description                                      | Number | MedDRA® High-Level Terms                       | Number |
|--------------|--------------------------------------------------------|--------|-----------------------------------------------|--------|
| Ziprasidone  | Suicidal and self-injurious behavior                   | 61     | Neurological signs and symptoms NEC           | 319    |
| Ziprasidone  | General signs and symptoms NEC                         | 53     | Disturbances in consciousness NEC             | 41     |
| Ziprasidone  | Neurological signs and symptoms NEC                    | 47     | Ventricle arrhythmias and cardiac arrest      | 41     |
| Ziprasidone  | Behavior and socialization disturbances                | 52     | Anxiety symptoms                              | 283    |
| Ziprasidone  | Neurological signs and symptoms NEC                    | 47     | Neurological signs and symptoms NEC           | 35     |
| Ziprasidone  | Anxiety symptoms                                       | 41     | Disturbances in consciousness NEC             | 280    |

**TABLE 9: Number and Type of Events in Each Population for Major Drugs Organized by MedDRA® High-Level Terms**

NEC: not elsewhere classified
Discussion

Overall, it was evident that both the frequencies and types of adverse events found in the adult population do not fit the distribution found in the pediatric or geriatric populations. As has been seen in prior studies, diabetes mellitus was frequently the most commonly reported adverse event in adults [10], but this was not the case for either the pediatric or geriatric populations. One possible explanation for this is that since adults are more likely than children to have impaired fasting glucose in the first place (often due to a longer exposure to certain physiologic factors, such as obesity and a sedentary lifestyle), they may be more predisposed to developing this complication. On the other hand, "weight increase" was frequently a top-five adverse effect for the major antipsychotic medications in children, consistent with prior meta-analyses [11]. Children were also more likely to exhibit side effects, such as "aggression," "abnormal behavior," and "suicidality," cognitive effects that may be seen more often in the developing brain. In particular, suicide attempts have previously been linked to antipsychotics in children with the AERS database [12]. For the geriatric population, neurological side effects, such as "confusional state" and "somanolence," figured more prominently. This suggests that the elderly, who are predisposed to neurological problems, may be more severely affected by the neurological sequelae of antipsychotics. In fact, the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer’s Disease (CATIE-AD) trial, studying elderly patients with Alzheimer’s disease, showed that atypical antipsychotics were associated with worsening cognitive function comparable to an additional year’s worth of cognitive decline compared to placebo [13].

Although we also analyzed differences in high-level terms between pediatric, adult, and geriatric populations, we realized that going to the next higher level grouping for MedDRA terms was not particularly illustrative. For instance, how does one distinguish "Neurological signs and symptoms" from "Disturbances in consciousness," and what exactly constitutes "General signs and symptoms?" These were among the most commonly reported high-level terms.

Our analysis of the literature revealed that there were adverse events that frequently had reports in AERS; yet, these events were not commonly mentioned in the literature. In the adult population, amongst the top five adverse events for the seven major antipsychotics, only pancreatitis in patients taking quetiapine had fewer than five reports in the literature. The analyses for the pediatric and geriatric populations generated comparatively more adverse events that were not commonly found in the literature. The result for quetiapine in the geriatric population is interesting, given reports of its association with pneumonia [14].

The limitations of the FDA AERS database include the lack of information on the number of individuals taking the various antipsychotic medications in each age group, which could have served as a "denominator" in our study. Due to this lack of a denominator, when comparing the total number of adverse events across the pediatric, adult, and geriatric populations, it was difficult to determine whether variations in the relative distribution of adverse events between the three age groups was truly due to differences in the rate of adverse events rather than simply variations in prescription frequency. For instance, this could be related to prescription trends or when the medications were released. Fortunately, the issue of a denominator was not problematic when comparing the particular side effect profile between the three populations for any given drug. Another issue is the fact that the correlation of a particular medication with an adverse event does not necessarily prove causation. For instance, an individual who is prone to a particular adverse event may be more likely to take an antipsychotic. Another potential problem is recall bias, as a physician who knows a patient is taking a given drug may be more likely to report adverse events that are widely known to be associated with that drug. Nevertheless, the sheer volume of the AERS database and its vast scope make it a useful tool for studying drug-related adverse events.

Conclusions

Overall, we were able to show that there are significant differences in both the numbers and types of adverse events between the pediatric, adult, and geriatric populations. In addition, this study offers a number of drug and adverse event combinations for follow-up analysis. Given the fact that these medications were overwhelmingly tested on the adult population and are commonly prescribed off-label, it is imperative that clinicians remain mindful of these differences when prescribing these medications in populations for whom the drugs were never formally tested.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.
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