An opportunity for clinical pharmacology trained physicians to improve patient drug safety: A retrospective analysis of adverse drug reactions in teenagers [version 1; referees: 2 approved with reservations]

Andy R. Eugene, Beata Eugene

Abstract

Background: Adverse drug reactions (ADRs) are a major cause of hospital admissions, prolonged hospital stays, morbidity, and drug-related mortality. In this study, we sought to identify the most frequently reported medications and associated side effects in adolescent-aged patients in an effort to prioritize clinical pharmacology consultation efforts for hospitals seeking to improve patient safety.

Methods: Quarterly reported data were obtained from the United States Food and Drug Administration Adverse Events Reporting System (FAERS) from the third quarter of 2014 and ending in the third quarter of 2017. We then used the GeneCards database to map the pharmacogenomic biomarkers associated with the most reported FAERS drugs. Data homogenization and statistics analysis were all conducted in R for statistical programming.

Results: We identified risperidone (10.64%) as the compound with the most reported ADRs from all reported cases. Males represented 90.1% of reported risperidone cases with gynecomastia being the most reported ADR. Ibuprofen OR=188 (95% CI, 105.0000 – 335.000) and quetiapine fumarate OR=116 (95% CI, 48.4000 – 278.000) were associated with the highest odds of completed suicide in teenagers. Ondansetron hydrochloride OR=7.12 (95% CI, 1.59 – 31.9) resulted in the highest odds of pneumothorax. Lastly, olanzapine (8.96%) represented the compound with the most reported drug-drug interactions cases, while valproic acid OR=221 (95% CI, 93.9000 – 522.000) was associated with the highest odds of drug-drug interactions.

Conclusion: Despite any data limitations, physicians prescribing risperidone in males should be aware of the high rates of adverse drug events and an alternative psychotropic should be considered in male patients. Further, patients with a history of pneumothorax or genetically predisposed to pneumothorax should be considered for an alternative antiemetic to ondansetron hydrochloride, due to increased odds associated with the drug and adverse event.

Keywords

adverse drug reactions, pharmacogenomics, psychiatry, precision medicine, pharmacogenomics, consult, mental health, teenagers
Introduction

When considering the aims of precision medicine, which has the underlying theme of maximizing therapeutic efficacy while minimizing adverse drug reactions, all physician and surgeon specialists provide an integral part in achieving the overall goal of this national endeavor (Manolio, 2016; Rasmussen-Torvik et al., 2014; Weintrilboum & Wang, 2017). Within medical specialties, clinical pharmacologists are vital for providing pharmacogenomics consultations to patients, other specialists, and in academic medicine to support the widespread implementation of pharmacogenomics and personalized medicine (Borobia et al., 2018; Moore, 2001; van der Wouden et al., 2017). Further, there is a growing need to provide more genomic medicine training modules to physicians in non-academic medical centers and rural clinics to support patient care decisions that address pharmacogenomics (McCauley et al., 2017). Within the United States, the American Board of Clinical Pharmacology (ABCP) accredits institutions that train clinical pharmacologists who consult on patient cases of drug-gene interactions (i.e. pharmacogenomics), drug-drug interactions (DDIs), drug-drug-gene interactions, toxicology cases, and the use of pharmacometric tools that provide Bayesian dosing support for therapeutic drug monitoring (TDM) (Aronson, 2012; Lewis & Nierenberg, 2007). However, when implementing hospital-based clinical pharmacology consultation units, aside from the established drug-gene guidelines, what is a reasonable approach for hospital pharmacologists to prioritize medications that are associated with the most reported adverse drug reactions that will improve hospital safety outcomes?

It is well-known that thousands of adverse drug reactions resulting in hospitalizations, increased lengths of hospital stay, and complications in patient management occur every year (Montané et al., 2018; Schmiedt et al., 2014). However, an approach that systematically addresses the top medications associated with the most reported adverse drug events, leading to a prioritization method for hospital pharmacologists to improve medication safety, is lacking (Davies et al., 2009; Shepherd et al., 2012). Several healthcare institutions in the United States have well established physician clinical pharmacology training programs, and integrate experiences into daily patient care, medical education, and research (Lewis & Nierenberg, 2007). The University of Chicago Hospital, in conjunction with the Indiana Institute for Personalized Medicine at the Indiana University, offers a clinical pharmacology consultation service that conducts pharmacogenomic consults to low-income patients and provides thorough documentation of its process in a 2016 publication (Eadon et al., 2016). Other ABCP-accredited institutions (e.g. Mayo Clinic, Johns Hopkins Hospital, Baylor College of Medicine, Cincinnati Children’s Hospital, and more) are training and leading the U.S. with various pharmacogenomics implementation strategies into routine patient care (see ABCP training programs).

In European nations and other countries with national health systems, the intrinsic goal of keeping all healthcare-related costs to a minimum and hospital re-admissions rates to a low, while still maintaining high-quality patient care, medical doctors specializing in clinical pharmacology who provide personalize medicine services are the norm (Borobia et al., 2018; Janković et al., 2016; Zagorodnikova Goryachkina et al., 2015). Contrastingly, the multi-payer model currently within U.S. hospitals, often preclude hospitals from absorbing the cost of a clinical pharmacologists who would translate pharmacogenetics guidelines into daily patient care.

It is important to note that hospitals with clinical pharmacology training programs are often ranked among the top ranked by U.S. news and world reports, even though clinical pharmacology is not one of the specialties being assessed for survival, patient safety, other care-related outcomes, and expert opinion (Harder et al., 2017). The service and commitment to the use of precision dosing in patient care, research, clinical pharmacology education, and pharmacogenomics implementation at these hospitals provide an overall compelling story. One of the most well recognized hospitals, globally, is the Karolinska Institutet in Stockholm, Sweden, due its awarding of the Nobel Prize in Physiology or Medicine. A recent article by the Karolinska Institutet discusses how the 50 year jubilee was recently celebrated in recognition of the establishment of their hospital’s Department of Clinical Pharmacology (Eichelbaum et al., 2018).

In the recent jubilee article, the Karolinska Institutet’s clinical pharmacologists detail the various established responsibilities of their clinical pharmacology services, which function as a division within the department of laboratory medicine today, and how they addressed this vital unmet clinical need within their medical center (Eichelbaum et al., 2018). In the U.S., a National Provider Identifier taxonomy code for clinical pharmacology is well established as 208U00000X; however, hospitals and state medical boards have not worked with state legislative officials to create a bill enacting medical licensure (e.g. independent, collaborative, or institutional) specifically for medical school graduates who enter directly into clinical pharmacology training. Yet, adverse drug reactions continue to affect outcomes and patient safety metrics each year (Burkhart et al., 2015; Montané et al., 2018).

It is important to realize that collaborative practice agreement laws between licensed physicians and pharmacists, physician assistants, and nurses are already in existence, but remains un-addressed for medical school graduates who choose only to specialize and train in clinical pharmacology. Therefore, if nothing is done, national implementation of precision medicine remains a challenge, due to not having enough trained medical doctors who focus on implementing pharmacogenomics into patient care and contribute to pharmacogenomics education (McCauley et al., 2017; Rosenman et al., 2017).

With this information as a background, the primary aim of this article is to determine the most frequently reported drugs and associated adverse drug reactions that are found within the FDA Adverse Events Reporting System (FAERS) that will aid in prioritizing efforts for clinical pharmacology consultation services. To do so we will access publicly available FAERS data and report reporting frequencies and reporting odd-ratios of
cases in an adolescent patient age group to avoid polypharmacy, albeit not exclusively in all cases.

Methods

Data
The United States Food and Drug Administration’s (FDA) Adverse Events Reporting System (FAERS) quarterly reports were downloaded, with dates ranging from the third quarter of 2014 to the third quarter of 2017. The ‘primaryid’ column, which represents a unique number of case sequence identifiers and manufacturer version number, were systematically linked as the primary field to other individual data files. Prior to our retrospective data analysis, we removed duplicate cases and selected reports classified from the adolescent age group alone. A source of bias in the FAERS quarterly files may be underreporting of drugs in particular people groups due to language. Institutional Review Board approval was not required due to the FAERS data being public de-identified patient cases.

The following are the data tables for each quarter (i.e. Q1-Q4) of the year (i.e. yy in the files): patient demographic and administrative information (DEMOyyQ1-Q4), drug/biologic information (DRUGyyQ1-Q4), the Medical Dictionary for Regulatory Activities (MedDRA) terms of reported adverse events (REACyyQ1-Q4), patient outcomes (OUTCyyQ1-Q4), report sources (RPSRyyQ1-Q4), drug therapy start dates and end dates (THERyyQ1-Q4), and finally the MedDRA terms coded for the clinical indications (INDIyyQ1-Q4). Links to data used can be found in Table 1.

Mapping of Drug-Gene Targets
The primary and secondary molecular target mappings of the top FAERS reported drugs were obtained from the compounds listed in the GeneCards database. We mapped the top ten genes using the GeneCards methodology, as has been previously reported (Stelzer et al., 2016; Weizmann Institute of Science, 2016).

Statistics
All data homogenization and statistics were computed using R for Statistical Computing (version 3.3.2, Vienna, Austria) programming software (R Core Team, 2015). The top 15 indications, adverse drug reactions, and drugs are reported for the adolescent age group. The frequency tables were calculated based on: (number of drugs or adverse effect events) / (number of patient records) = drug or adverse events frequency. The reporting odds-ratios (OR), that scans across the medications under test, for a particular reported adverse drug event, are calculated using “Diarrhoea” as the control preferred term while “Hyperglycaemia”, “Pneumothorax”, and “Completed suicide” preferred terms were used for cases. The glm() function and binomial statistical family in R were used to conduct the logistic regression analysis. Odds-ratios are reported as: odds-ratio, lower-95% confidence-interval (CI), upper-95% CI, and p-value. A p-value of less than 0.05 was considered to be statistically significant.

Results
The study included a total of 6,141 unique cases (male=2,938, female=3,021, undefined=184) for adolescent-aged patient records, out of a total of 22,784 unique pediatric cases. The compound with the most reported adverse drug reactions was risperidone (n=788) representing 10.64% of all reported cases. We found that of the reported risperidone cases, 90.1% (male=710, female=3021, undefined=184) for adolescent-aged patient group. The frequency tables were calculated based on: (number of drugs or adverse effect events) / (number of patient records) = drug or adverse events frequency. The reporting odds-ratios (OR), that scans across the medications under test, for a particular reported adverse drug event, are calculated using “Diarrhoea” as the control preferred term while “Hyperglycaemia”, “Pneumothorax”, and “Completed suicide” preferred terms were used for cases. The glm() function and binomial statistical family in R were used to conduct the logistic regression analysis. Odds-ratios are reported as: odds-ratio, lower-95% confidence-interval (CI), upper-95% CI, and p-value. A p-value of less than 0.05 was considered to be statistically significant.

Table 1. Data used in this study are referenced from the U.S. Food and Drug Administration’s quarterly reported adverse events reporting system data.

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PRL (Prolactin; 25.59), HTR2A (5-hydroxytryptamine receptor 2A; 21.38), CYP2D6 (cytochrome P450 Family 2 Subfamily D Member 6; 20.21), HTR2C (14.32), ABCB1 (ATP binding cassette subfamily B member 1; 13.63), BDNF (brain derived neurotropic factor; 11.93), DRD3 (11.79), HTR1A (11.35), and CYP3A5 (11.03). Figure 1 illustrates the reporting frequencies of the top 15 reported drugs in adolescents.

The most commonly reported clinical indication was prophylaxis (12.82%), followed by acute lymphocytic leukemia (6.55%), and product used for unknown indication (6.44%). Figure 2a illustrates the reporting frequencies of the top fifteen reported clinical indications in the adolescent patient records from our study. The most reported adverse drug reaction was diarrhea (n=110, male=55, female=53, undefined=2) which represented 4.62% of the all of the reported cases. Following diarrhea, hyperglycemia (n=45, male=35, female=10) was the second most reported adverse event drug representing 4.43% of all reported cases. Figure 2b illustrates the reporting frequencies of the top fifteen reported adverse drug reactions for all adolescent cases.

We conducted logistic regression and reported odds-ratios (OR) by setting the control variable to the most commonly reported adverse event, diarrhea (4.62%) and tested the second most common ADR, hyperglycemia (4.43%) and subsequently a rather specific adverse drug reaction such as pneumothorax (3.91%, n=12, male=6, female=6). We found that risperidone OR=214 (95% confidence interval CI, 148 – 308, p=7.82e-24), risperidone OR=71.0 (95% CI, 41.4000 – 122.000, p=4.17e-54), diphendydramine OR=46.1 (95% CI, 23.6000 – 90.000, p=3.56e-29), lorazepam OR=6.08 (95% CI, 4.0500 – 9.130, p=3.25e-18), and tacrolimus OR=4.28 (95% CI, 2.7300 – 6.710, p=2.45e-10); while amlodipine besylate OR=0.213 (95% CI, 0.1260 – 0.361, p=9.17e-09) was associated with diarrhea in this drug grouping. Figure 4a illustrates the frequencies for the top fifteen reported medications associated with drug-drug interactions.

We identified that the top three medications associated with drug-drug interactions (n=182, male=85, female=97) were olanzapine (8.96%), lorazepam (8.08%), and risperidone (5.36%). The odd-ratios for drugs reported to cause drug-drug interactions were found to be: valproic acid OR=221 (95% CI, 93.9000 – 522.000, p=6.20e-35), diazepam OR=170 (95% CI, 62.6000 – 463.000, p=7.82e-24), risperidone OR=71.0 (95% CI, 41.4000 – 122.000, p=4.17e-54), diphendydramine OR=46.1 (95% CI, 23.6000 – 90.000, p=3.56e-29), lorazepam OR=6.08 (95% CI, 4.0500 – 9.130, p=3.25e-18), and tacrolimus OR=4.28 (95% CI, 2.7300 – 6.710, p=2.45e-10); while amlodipine besylate OR=0.213 (95% CI, 0.1260 – 0.361, p=9.17e-09) was associated with diarrhea in this drug grouping. Figure 4a illustrates the frequencies for the top fifteen reported medications associated with drug-drug interactions.

Figure 1. Frequencies for the top 15 reported drugs in adolescent patient records identified in the FDA Adverse Events Reporting system ranging from the 3rd quarter of 2014 to the 3rd quarter of 2017.
Figure 2. Frequencies for the top 15 reported (a) clinical indications and (b) adverse drug reactions (ADRs) in adolescent patient records identified in the FDA Adverse Events Reporting system ranging from the 3rd quarter of 2014 to the 3rd quarter of 2017.
Figure 3. Frequencies for the top 10 reported (a) adverse drug reactions and (b) reported clinical indications for risperidone in adolescent patient records identified in the FDA Adverse Events Reporting system ranging from the 3rd quarter of 2014 to the 3rd quarter of 2017.
Figure 4. Frequencies for the top 15 reported (a) medications associated with drug-drug interactions (DDIs) and (b) completed suicide in adolescent patient records identified in the FDA Adverse Events Reporting system ranging from the 3rd quarter of 2014 to the 3rd quarter of 2017.
In assessing the odds-ratios for completed suicide, with a control of diarrhea, among the top twenty associated drugs with completed suicide (n=34, male=8, female=23, undefined=3), we found that ibuprofen OR=188 (95% CI, 105.0000 – 335.000, \( p=4.17e-70 \)) resulted in the highest odds in adolescent cases. Further, we also found, in order of decreasing odds: quetiapine fumarate OR=116 (95% CI, 48.4000 – 278.000, \( p=1.43e-26 \)), diazepam OR=86.0 (95% CI, 32.8000 – 225.000, \( p=1.15e-19 \)), certirizine hydrochloride OR=59.1 (95% CI, 27.9000 – 126.000, \( p=2.33e-26 \)), diphenhydramine OR=16.5 (95% CI, 8.6800 – 31.300, \( p=1.12e-17 \)), and risperidone OR=4.48 (95% CI, 2.2700 – 8.820, \( p=1.49e-05 \)) also were associated with increased odds of completed suicide within adolescent cases.

Contrastingly, hydroxyzine hydrochloride OR=0.0946 (95% CI, 0.0595 – 0.150, \( p=2.08e-23 \)) and lorazepam OR=0.254 (95% CI, 0.1410 – 0.458, \( p=5.15e-06 \)) were found to be associated with increased the odds for diarrhea, among top twenty compounds tested for completed suicide. Neither mirtazapine (\( p=0.980 \)) nor herbalists (\( p=0.990 \)) were associated with increased odds of completed suicide, despite being listed as second and fourth in associated frequency. Similarly, acetaminophen/valbutal-bital (\( p=0.996 \)), acetaminophen/hydrocodone (\( p=0.996 \)), alco-hol (\( p=0.996 \)), atorvastatin calcium (\( p=0.996 \)), carbamazepine (\( p=0.996 \)), fluoxetine hydrochloride (\( p=0.993 \)), mirtazapine (\( p=0.980 \)), paroxetine hydrochloride (\( p=0.995 \)), and quetiapine (\( p=0.976 \), in contrast to quetiapine fumarate \( p=1.43e-26 \)) did not increase odds of completed suicide, in our analysis. Figure 4b depicts the top fifteen drugs associated with completed suicide in adolescent patient records identified in the FAERS.

The top ten genes associated with ibuprofen, the compound with the highest odds for completed suicide, in this study were found to be PTGS2 (prostaglandin-endoperoxide synthase 2; 32.79), PTGS1 (22.74), ALB (albumin; 16.90), CYP2C9 (16.71), ILB (interleukin 1 beta; 15.59), OXAlL (OXAlL mitochondrial inner membrane protein; 14.28), IL6 (13.12), IL10 (12.83), CYP2C8 (12.64), and ILIRN (11.82).

Discussion

In this study, we chose the adolescent data, over the adult and elderly age groups, in efforts to minimize polypharmacy and to address the scope of the primary aim of our study. We identified pharmacogenes associated with drugs reported with adverse drug reactions and serves as a guide for clinical pharmacology services to prioritize medications in both the inpatient and outpatient care setting. We found that risperidone, a second-generation antipsychotic, with FDA-approval for managing schizophrenia, bipolar I disorder (acute manic/mixed), autistic disorder associated irritability, and Tourette’s syndrome in pediatrics represented the most reported drug in teenagers. We also found that two of the top three most frequently reported indications for risperidone, in adolescent cases, were indications which are not FDA-approved – attention deficit/hyperactivity disorder (12.51%) and depression (7.79%). Thus, suggesting the need for an increase in clinical pharmacology-trained physicians to help facilitate the pressing clinical need for precision medicine in psychiatry where diagnoses are stratified by biologically and physiologically relevant symptoms and then subsequent treatments are implemented based on drug pharmacokinetics (i.e. absorption, metabolism, distribution, and elimination) and pharmacodynamics (Boorstein & Historian, 2018).

Prednisolone sodium succinate (3.81%), an anti-inflammatory glucocorticoid with various indications, and the anti-tumor necrosis factor-\( \alpha \) (TNF- \( \alpha \)) monoclonal antibody – infliximab (3.35%), were second and third in reporting frequency for adolescent patients, respectively. More precise dosing of infliximab may be achieved by pharmacologists using pharmacometrics methods that utilize measured plasma concentrations to recommend doses and dosing intervals to avoid sub-therapeutic concentrations.

In reference to our results suggesting increased odds of pneumothorax with ondansetron hydrochloride, patients who have a history of pneumothorax, or have conditions with known increased prevalence of pneumothorax (e.g. Marfan’s syndrome, Ehlers-Danlos syndrome, rheumatoid arthritis, poly- and dermatomyositis, ankylosing spondylitis, systemic sclerosis) should be managed with an alternative antiemetic. Further, additional studies should be pursued investigating the mechanisms connective tissue diseases and gene expression modulation with ondansetron.

Approximately nine of the top fifteen reported drugs associated with DDIs, shown in Figure 4a, are prescribed in patients treated for mental health disorders. It may be that patients are experiencing the compounded effects of multiple prescriptions medications competing for the same hepatic biotransformation pathways, coupled with a loss-of-function SNP affecting the primary drug-gene pathway, rather than the later alone (Storelli et al., 2018). Therefore, these drug-drug-gene interactions resulting in phenocconversion, from a normal metabolizer to a poor or intermediate metabolizer, is an important consultation area for clinical pharmacologists. Similarly, this is another area where the use of TDM and Bayesian dosing support with pharmacometrics may be the most efficient method (Hiemke et al., 2011; Polasek et al., 2018).

The limitations and strength of the FDA Adverse Events Reporting System database is that the reports are voluntarily submitted by physicians, pharmacists, lawyers, patient consumers, and various healthcare professionals. Therefore, a limitation is that the complete medical histories are not factored into the analysis and the results are indicative of a subset of all patient adverse drug event experiences. However, despite the limitations, the FAERS database provides insight to the importance of publicly available pharmacovigilence data that allows open analysis, discovery for potential repurposing of existing drugs, and provides a reporting mechanism for patients and caregivers to share their medication experiences (Burkhart et al., 2015; Oshima et al., 2018).

Conclusion

In addition to established pharmacogenomic guidelines, the FAERS database provides an important reference point for
clinical pharmacologists to use when prioritizing medication safety consultations, pharmacogenomic education, and when seeking to improve hospital outcomes.

**Data availability**
Data used in this study is available from the United States Food and Drug Administration (FDA) website, with specific links provided in Table 1.

**References**


Data availability
The author(s) declared that no grants were involved in supporting this work.

**Competing interests**
No competing interests were disclosed.

**Publisher Full Text**
Open Peer Review

Current Referee Status: ? ?

Version 1

Referee Report 16 July 2018
doi:10.5256/f1000research.16298.r35300

Daniel D Hawcutt
Department of Women's and Children's Health, University of Liverpool, Liverpool, UK

This is an interesting retrospective review of ADR reports submitted to the US FDA for adolescents.

The strengths are that this population are rarely considered independently, despite having their own health needs and (as noted by the authors) not having quite the severity of polypharmacy as older individuals. Also, the study considers pharmacogenomics related to the most commonly prescribed medicines, using genecards website as the data source.

There is a lot of useful data contained in this publication, however there are some aspects that I think could be improved by some clarifications:

1) What does a genecard score mean for a gene? I know a link is given, but sentence or two giving an overview would help the reader.

2) I am uncomfortable about the odds ratios (ORs) for the completed suicide that feature prominently in the results section of the main paper and the abstract (as they are very very large ORs). Are these describing young people who used the drug as the means to commit suicide, or committed suicide while incidentally using this medication (two very different populations). While I appreciated the lack of medical history mentioned in the discussion, I do worry that presenting these finding when compared to diarrhoea may make the drugs look more dangerous than they are (and I have indicated that professional statistical advice would be useful here to clarify this point - is diarrhoea the right comparator, or should it be something else?).

3) Phrases like "need for precision medicine in psychiatry" in the discussion sound as if they suggest the study has identified new (or overlooked) pharmacogenomic associations that a clinical pharmacologist could act on, but unless I have misunderstood, the study does not do this, it only highlights where areas of unmet pharmacogenomic need exist. The pharmacogenomic section could be removed from the paper and it would still be a good paper, but assuming it is kept, then I think it needs to clearer exactly what information this brings to a clinician.

Overall, I enjoyed this paper, and it adds to this field.

Is the work clearly and accurately presented and does it cite the current literature?
Yes
Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Pediatric Pharmacology and pediatric pharmacogenomics

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Referee Report 26 June 2018

doi:10.5256/f1000research.16298.r35025

Antonio J. Carcas

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The aim of this study is to know the most frequently reported drugs associated to adverse drug reactions (and DDIs) in order to prioritize the efforts for clinical pharmacology consultation services. I find this manuscript interesting.

Comments:

Just to clarify, please confirm that adolescent age is considered from 12 to 17 yo.

I agree about the utility of knowing the most frequently reported drugs associated to adverse drug reactions; the author should mention some other similar studies previously published\(^1\)-\(^4\). I also like the concept that a better knowledge of the most frequent drugs producing AEs can drive prioritization of efforts for clinical pharmacology consultation services. However:

- Authors should give a more detailed description of the design (case/non-case ?) and statistical methods allowing calculation of OR.
- We should not disregard the potential of this analysis to rise hypothesis about the link between the AE, DDIs and drug PK and pharmacogenetics. A comment by the authors would be useful.
- I also think that it would be useful for readers to provide a more specific comment about the relationship between pharmagenomics and AEs whose knowledge could improve drug safety. For example, CYP2D6 polymorphisms have been related to weight gain and hyperprolactinemia in patients with risperidone (including adolescents). On the other side, the association of ondansetron with pneumothorax could be a confounding by indication and not a true causal association.

Although not new, it is interesting also the finding that frequently reported indications for risperidone were non-approved indications by FDA and that top fifteen reported drugs associated with DDIs are prescribed in patients treated for mental health disorders.

References

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
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