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Psychosis as an adverse effect of antibiotics

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A R T I C L E   I N F O

A B S T R A C T

Adverse neuropsychiatric effects of antibiotic medications have been well documented. There is evidence suggesting a direct relationship between acute psychosis and antibiotic exposure. Conversely, the tetracycline antibiotic minocycline has been associated with improvements in psychopathology in patients with psychotic disorders. The purpose of the present study was to investigate the prevalence of spontaneously reported adverse drug reactions (ADRs) of psychotic symptoms in adults for antibiotics and the odds of psychosis compared to minocycline for individual antibiotics and antibiotic classes. We searched the publicly available U.S. F.D.A. Adverse Event Reporting System (FAERS) from inception through March 2020 for which an antibiotic was the suspected agent of an adverse drug reaction (ADR). We investigated 23 different antibiotics, comprising 183,265 adverse event reports and 2955 psychosis ADRs. For individual antibiotics, the prevalence of psychosis ADRs ranged from 0.3 to 3.8%. Fifteen antibiotics were associated with a significantly increased odds of psychosis (OR = 1.67–9.48), including penicillins, fluoroquinolones, macrolides, cephalosporins, and doxycycline. Our results suggest that psychosis is a potential adverse effect of antibiotic treatment, but risks vary by specific agents. Future studies in this area are needed to identify specific underlying biological mechanisms that contribute to these associations. Findings may also inform on clinical decisions regarding the selection of antibiotic therapy in vulnerable patient populations.

1. Introduction

Adverse neuropsychiatric effects of antibiotic medications have been well documented (Zareifopoulos et al., 2017). Usually these side effects are reported when a patient is treated for an infection, and can range from milder symptoms such as insomnia to severe symptoms, including delirium and psychosis. Although some infections have been associated with acute psychosis, including urinary tract infections (Chae and Miller, 2015; Kehoe and Miller, 2020), there is also evidence suggesting a direct relationship between acute psychosis and antibiotic exposure (Mostafa and Miller, 2014). Conversely, minocycline, a tetracycline antibiotic with anti-inflammatory properties, has been associated with improvements in psychopathology in patients with psychotic disorders (Çakici et al., 2019). The mechanisms underlying associations between antibiotics and psychosis remain unclear, and may vary by antibiotic class. Potential hypotheses include direct effect of antibiotics on neurotransmitters and their receptors, as well as anti-inflammatory effects that may modulate cytokine production, thereby impacting neurotransmitter function. Regarding the latter hypothesis, we previously found evidence for psychosis as an adverse effect of monoclonal antibody immunotherapy, particularly for agents that suppress the immune system (particularly targeting adaptive immunity) and are used to treat autoimmune disorders (Essali et al., 2019). To our knowledge, no previous studies have systematically investigated risks of psychosis as an adverse effect of antibiotics. The purpose of the present study was to investigate the prevalence of spontaneously reported adverse drug reactions (ADRs) of psychotic symptoms in adults for antibiotics and the odds of psychosis compared to minocycline for individual antibiotics and antibiotic classes.

2. Methods

2.1. Data sources

The U.S. F.D.A. Adverse Event Reporting System (FAERS) is a publicly available database that contains adverse event reports, medication error reports. and product quality complaints resulting in adverse events that were submitted to the F.D.A. These reports are voluntarily submitted by healthcare professionals and consumers. If manufacturers receive such a report, they are required to send these reports to the F.D.A. The informatic structure of the FAERS database adheres to the international

safety reporting guidance issued by the International Conference on Harmonisation (ICH E2B). Adverse events and medication errors are coded using terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. We included all reports in FAERS from inception through March 2020 for which an antibiotic was the suspected agent of the adverse event.

2.2. Procedures

Spontaneously reported adverse events were identified by searching each antibiotic in FAERS. We included data on adults age 18–64 for all antibiotics, as psychosis is a relatively rare phenomenon in children and adolescents, and psychosis in the elderly may be confounded by an increased prevalence of general medical conditions. Psychiatric adverse events were included as a subheading in the search results for individual antibiotics. The following terms listed in FAERS were counted as possible psychosis adverse events: hallucinations (auditory, visual, olfactory, gustatory, tactile, somatic, mixed, unspecified), delusions (persecutory, grandiose, unspecified), flat affect, catatonia, paranoia, psychotic symptom and psychotic behavior. We combined the data from the most commonly reported generic and brand formulations of each antibiotic. Data on the total number of adverse events, number of psychiatric adverse events, and number of psychosis adverse events for each antibiotic were extracted by one author (NE) and independently verified by another author (BJM).

2.3. Statistical analysis

For each antibiotic, we first calculated the proportion of ADRs for psychosis by dividing the number of psychosis ADRs by the total number of ADRs. We then calculated odds ratios (OR) and 95% confidence intervals (95% CIs) for total psychosis ADRs and total hallucination ADRs relative to minocycline. We chose minocycline as the comparator

antibiotic because of evidence for its potential efficacy in the treatment of patients with psychosis (Çakici et al., 2019). P-values were considered statistically significant at the $\alpha = 0.05$ level if the 95% CI for the OR excluded 1.00. All statistical analyses were performed in Stata 10.0 (StataCorp LP, College Station, TX).

3. Results

We investigated ADRs for 23 different antibiotics, for which 183,265 adverse events were reported. 19,628 (10.7%) of the ADRs were psychiatric, including 2955 psychosis ADRs. Therefore, psychosis ADRs comprised 15% of the psychiatric ADRs, and 1.6% of all ADRs. For individual antibiotics, the prevalence of psychosis ADRs ranged from 0.3 to 3.8%.

As shown in Table 1, compared to minocycline, 15 of the 23 antibiotics were associated with a significantly increased odds of psychosis (OR = 1.67–9.48), including amoxicillin/clavulanate, ceftriaxone, SMX/TMP, cephalexin, azithromycin, doxycycline, nitrofurantoin, erythromycin, cefuroxime, amoxicillin, cefepime, levofloxacin, metronidazole, ciprofloxacin, and clarithromycin. 6 of the 23 antibiotics showed non-significant increased odds of increased psychosis, including tetracycline, clindamycin, amikacin, piperacillin, penicillin, and meropenem. By contrast, 2 of the 23 antibiotics were associated with a non-significantly decreased odds of psychosis compared to minocycline; vancomycin (OR = 0.80, 95% CI 0.46–1.39) and gentamicin (OR = 0.81, 95% CI 0.36–1.82). In a post-hoc analysis, we calculated ORs only for hallucinations (in any sensory modality) as this was the most reported psychotic ADR, which did not change the pattern of findings. As a class, compared to minocycline, there was a significant increased odds of psychosis for other tetracyclines (OR = 2.23), penicillins (OR = 2.15), fluoroquinolones (OR = 6.11), macrolides (OR = 7.04), and cephalosporins (OR = 2.25), but not aminoglycosides.

Table 1
Odds ratios for psychosis adverse drug reactions for individual antibiotics and antibiotic classes, relative to minocycline.

| Drug | | Adverse Event | | | | | | | | | |
| Class | Agent | Total | Psychotic Symptoms | | | | | Hallucinations | | | |
			% ADR	N	Male (n)	OR	95% CI	N	Male (n)	OR	95% CI
Tetracycline	Minocycline	5149	0.4	21	6	1.00	Reference	13	4	1.00	Reference
	Doxycycline	6237	0.9	59	31	**2.32**	**1.41–3.82**	32	11	**2.03**	**1.07–3.88**
	Tetracycline	996	0.7	7	0	1.72	0.73–4.06	4	0	1.59	0.52–4.89
	All Tetracyclines	7233	0.9	66	31	**2.23**	**1.36–3.66**	36	11	**1.97**	**1.04–3.72**
Sulfonamides	SMX/TMP	22,697	0.7	168	80	**1.81**	**1.15–2.86**	134	62	**2.34**	**1.32–4.14**
Nitrofurantoin	Nitrofurantoin	3300	0.9	32	8	**2.38**	**1.37–4.13**	25	8	**3.00**	**1.53–5.87**
Penicillin	Penicillin	877	0.5	5	1	1.40	0.53–3.72	3	0	1.35	0.39–4.76
	Amoxicillin	10,658	1.2	129	51	**2.97**	**1.87–4.71**	86	34	**3.20**	**1.78–5.73**
	Amoxicillin/Clavulanate	15,552	0.6	106	46	**1.67**	**1.05–2.67**	74	27	**1.88**	**1.04–3.40**
	Piperacillin	530	0.5	3	0	1.39	0.41–4.67	1	0	0.75	0.10–5.72
	All Penicillins	27,617	0.8	243	98	**2.15**	**1.38–3.37**	164	61	**2.35**	**1.33–4.14**
Fluoroquinolone	Levofloxacin	26,957	2.2	619	193	**5.63**	**3.64–8.71**	421	126	**6.19**	**3.56–10.75**
	Ciprofloxacin	18,042	2.7	503	225	**6.84**	**4.41–10.59**	348	159	**7.64**	**4.39–13.30**
	All Fluoroquinolones	44,999	2.0	1122	418	**6.11**	**3.96–9.42**	769	285	**6.76**	**3.90–11.71**
Macrolides	Azithromycin	5272	0.8	46	21	**2.14**	**1.27–3.59**	31	15	**2.33**	**1.22–4.46**
	Erythromycin	4254	1.0	45	22	**2.59**	**1.54–4.36**	37	20	**3.44**	**1.83–6.49**
	Clarithromycin	18,356	3.8	710	271	**9.48**	**6.14–14.65**	439	169	**9.47**	**5.45–16.46**
	All Macrolides	27,882	2.8	801	314	**7.04**	**4.56–10.87**	507	204	**7.20**	**4.14–12.49**
Glycopeptides	Vancomycin	9787	0.3	32	21	0.80	0.46–1.39	24	16	0.97	0.49–1.91
Nitroimidazoles	Metronidazole	11,168	2.5	283	110	**6.21**	**3.98–9.69**	182	74	**6.45**	**3.67–11.34**
Lincosamide	Clindamycin	4604	0.4	19	9	1.01	0.54–1.88	16	7	1.38	0.66–2.86
Aminoglycoside	Gentamicin	2432	0.3	8	7	0.81	0.36–1.82	7	6	1.14	0.45–2.86
	Amikacin	1556	0.5	8	6	1.26	0.56–2.85	7	6	1.78	0.71–4.47
	All Aminoglycosides	3988	0.4	16	13	0.98	0.52–1.88	14	12	1.39	0.65–2.96
Carbapenem	Meropenem	3354	0.5	20	11	1.46	0.79–2.70	12	7	1.42	0.65–3.11
Cephalosporins	Cefuroxime	2352	0.5	41	16	**2.92**	**1.72–4.95**	29	13	**3.34**	**1.73–6.42**
	Ceftriaxone	6059	0.6	42	27	**1.70**	**1.01–2.87**	27	18	1.76	0.91–3.42
	Cefepime	1334	1.7	23	9	**4.23**	**2.33–7.66**	22	9	**6.53**	**3.28–13.00**
	Cephalexin	5799	0.8	47	8	**1.99**	**1.19–3.33**	35	4	**2.39**	**1.26–4.52**
	All Cephalosporins	16,636	0.9	153	60	**2.25**	**1.42–3.56**	113	44	**2.69**	**1.51–4.78**

4. Discussion

In the FAERS database, we found a 0.3–3.8% prevalence of psychosis ADRs from treatment with antibiotics. Many different antibiotics and antibiotic classes were associated with a significant, 1.7- to 9.5-fold increased odds of psychosis compared to minocycline. The pattern of findings was consistent between ADRs for all psychotic symptoms and hallucinations.

The antibiotics showing increased odds of psychosis are from various drug classes including penicillins, cephalosporins, fluoroquinolones, macrolides, and aminoglycosides. Those antibiotics with the greatest increased odds of psychosis were macrolides, fluoroquinolones and metronidazole. The mechanisms underlying associations between antibiotics and psychosis remain unclear, and may vary by antibiotic class. Clarithromycin, a macrolide, has GABA-A antagonistic properties which could contribute to epileptiform activity and thus direct CNS neurotoxic effects (Zareifopoulos et al., 2017). Another possible mechanism could be via increasing cortisol and prostaglandin levels or other drug levels via a CYP3A4 inhibitory effect, leading to increased neuropsychiatric adverse effects (Di Poggio et al., 2011). Fluoroquinolones have also been found to antagonize GABA-A receptors. This may possibly be related to the similarity of their structure to GABA, allowing them to compete at the receptors (Akahane et al., 1989). Additionally, fluoroquinolones are moderately lipophilic allowing them to readily penetrate the blood brain barrier and exert neurotoxic effects (Nau et al., 2010). Alternatively, fluoroquinolones may directly activate NMDA receptors, as one animal study found that blocking NMDA receptors in mice prevented the occurrence of fluoroquinolone-induced neurotoxicity (De Sarro et al., 1997). Metronidazole-induced neurotoxicity is also thought to be caused by its inhibitory effect on the GABA receptor. Additionally, MRI studies in patients receiving metronidazole showed evidence of cytotoxic and vasogenic edema, which could be another possible mechanism of its neurotoxicity (Kuriyama et al., 2011). Penicillins and cephalosporins have also been reported to exert GABA-A antagonistic effects, which may lead to excitatory activity, including-psychosis (Behrends, 2000). Aminoglycosides appear to act as NMDA receptor agonists, leading to excitotoxicity and *in vitro* neuronal cell death (Segal et al., 1999). On the other hand, in animal studies, tetracyclines have been shown to have anti-inflammatory, antioxidant, and anti-apoptotic properties in the CNS. Additionally, they regulate tissue and microglial response to injury (Faheem et al., 2019; Garrido-Mesa et al., 2013). This may explain the recent evidence regarding minocycline's beneficial use in psychotic disorders, however, it does not account for within class variability, as we found Doxycycline to be twice as likely to cause psychosis when compared to Minocycline. However, in-class variability in these properties have also been demonstrated, with minocycline showing higher neuroprotective effects (Yrjänheikki et al., 1998). This may be explained by the fact that minocycline is the most lipophilic of the tetracycline antibiotics which means it has higher BBB penetration. By contrast, doxycycline is less lipophilic and with less neuroprotective properties than minocycline, which may explain its increased odds of psychosis ADRs (Elewa et al., 2006). Minocycline also has up to six metabolites, some of which demonstrating antibacterial properties which could be enhancing its anti-inflammatory effect, whereas doxycycline has no known metabolites (Agwuh and MacGowan, 2006).

An important, non-mutually exclusive consideration is that the infection itself, not the antibiotic treatment, is associated with exacerbation of psychosis in some cases. Schizophrenia is associated with an increased prevalence of comorbid infections, notably urinary tract infections during episodes of acute psychosis (Graham et al., 2014; Miller et al., 2013), which may be a recurrent phenomenon (Laney et al., 2015). A meta-analysis found a 1.7-fold increase in positive *Toxoplasma gondii* IgM antibodies—a marker of acute/recent exposure or reinfection—in patients acute psychosis versus controls (Monroe et al., 2015). Several other studies have also found an increased prevalence of active viral (Ahokas et al., 1987; Krause et al., 2010; Srikanth et al., 1994) and

chlamydial (Fellerhoff et al., 2007) infections in patients with acute psychosis. However, these studies do not permit inferences regarding temporal or causal aspects of the association with acute psychosis. Nevertheless, Danish population-based samples have found associations between genetic susceptibility to infection and schizophrenia (Nudel et al., 2019), as well as a bidirectional association between schizophrenia and hospital contact for infection (Kohler-Forsberg et al., 2019; Nielsen et al., 2016).

Interestingly, the prevalence of psychosis ADRs in the present study (0.3–3.8%) was higher than the prevalence of psychosis ADRs associated with monoclonal antibodies (0.1–0.4%) in our previous study (Essali et al., 2019). There are several potential explanations for this discrepancy. One possibility is that antibiotics are more frequently used than monoclonal antibodies, and thus the estimates in the present study are more precise. Alternatively, monoclonal antibodies target only specific immune molecules and do not have off-target (i.e., non-immune) effects. Therefore, psychosis ADRs due to monoclonal antibodies would be attributable to their immune effects. By contrast, antibiotics have both immune and non-immune effects, and therefore associated psychosis ADRs may be attributable to a broader range of potential mechanisms. Lastly, we used the World Health Organization Vigibase database for the previous study, and the FAERS in the present work, although there is substantial overlap between these two databases. We also restricted ADRs to adults in the present study, whereas the publicly available version of Vigibase does not permit filtering of results by age.

There are several strengths to the present study. To our knowledge, ours is the first study to systematically investigate the prevalence of psychosis ADRs for individual antibiotics. In using a large database, like FAERS, it allows us to examine the presence of relatively rare adverse events such as psychosis. We also found a similar pattern of results for all psychotic symptoms and hallucination, which supports the consistency of findings. As with any study utilizing a public database, there are limitations. The FDA does not verify reports submitted to FAERS and does require the establishment of a causal relationship between the agent and adverse events. These reports maybe submitted by healthcare professionals or consumers, so there is a risk of misclassification of ADRs. There is also a risk of duplicate reporting as well as potential underreporting of adverse event is report. Individual level data on past psychiatric history and family history of psychosis are not available, which would shed light on potential confounding/moderating factors. Furthermore, the possibility that some subjects had a previous history of undiagnosed psychosis represents another potential residual confounding factor, and its effect on the observed associations is unclear. It is also important to note that the odds of psychosis ADRs would be different if a different antibiotic than Minocycline was chosen as the comparator, especially given its potential antipsychotic effects. In this regard, the absolute risk percentage for psychosis ADRs is an informative measure.

Taken together, our results suggest that psychosis is a potential adverse effect of antibiotic treatment, and risks vary by specific agents. Future studies in this area are needed to identify specific underlying biological mechanisms that contribute to these associations. Furthermore, findings may also inform on clinical decisions regarding the selection of antibiotic therapy in vulnerable patient populations (e.g., use of fluoroquinolones and macrolides in patients with psychotic disorders).

Declaration of competing interest

Dr. Essali has nothing to disclose. Dr. Miller has nothing to disclose for the present work. In the past 12 months, Dr. Miller received research support from Alkermes, Augusta University, NARSAD, the National Institute of Mental Health, and the Stanley Medical Research Institute; and Honoraria from Psychiatric Times.

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