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Reporting Patterns of Sialorrhea Comparing Users of Clozapine to Users of Other Antipsychotics

A Disproportionality Analysis Using VigiBase

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Abstract:

Background: Sialorrhea is a non-life-threatening, but potentially invalidating adverse drug reaction (ADR) in patients using clozapine. In light of the very serious ADRs (agranulocytosis and myocarditis), sialorrhea is at risk to be overlooked by health care professionals. In this study, the sialorrhea reporting patterns of clozapine compared with other antipsychotics were assessed by evaluating differences in relative reporting frequency and reporter type.

Methods: A case/noncase disproportionality analysis using data from VigiBase (1968–2016) was performed. Reports of antipsychotics with “salivary hypersecretion” as ADR were considered as cases, and those with ADRs other than salivary hypersecretion were defined as noncases. Relative reporting frequencies were expressed as reporting odds ratios (RORs), and multivariate logistic regression was performed with the drug-ADR pair as unit of analysis to estimate RORs with 95% confidence intervals (CIs).

Results: A total of 1,169,254 drug-ADR pairs from 425,304 unique Individual Case Safety Reports were identified. Sialorrhea was relatively more frequently reported in clozapine ($n = 2732$ [1.1%]) compared with other antipsychotics ($n = 2911$ [0.31%]; ROR, 3.60; 95% CI, 3.41–3.79) and was reported relatively more often by consumers (ROR, 19.8; 95% CI, 15.1–25.9) compared with health care professionals (ROR, 2.44; 95% CI, 2.27–2.63).

Conclusions: Sialorrhea was reported almost 4 times more often with clozapine use than with other antipsychotic use and was reported 8 times more often by patients than by health care professionals. This provides a signal of disproportion in sialorrhea occurrence among clozapine compared with other antipsychotics and in light of the disproportionality between reporter and an underreporting by health care professionals, underlining the importance to incorporate sialorrhea into the shared decision process when commencing clozapine therapy.

Key Words: adverse drug reactions, clozapine, sialorrhea, pharmacovigilance, disproportionality analysis

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Clozapine is an antipsychotic drug with distinct therapeutic advantages, including superior efficacy over other antipsychotics in refractory schizophrenia.¹ On the other hand, clozapine may cause many adverse drug reactions (ADRs) as a result of its broad pharmacological profile, and it is well known for its specific safety problems such as life-threatening agranulocytosis and myocarditis.² A frequently occurring non-life-threatening, but potentially socially invalidating ADR in patients using clozapine is sialorrhea or excessive salivation.³ The prevalence of sialorrhea among patients using clozapine has been estimated at 30% to 80%, rendering it the second most frequently occurring ADR of clozapine.⁴ Sialorrhea often occurs shortly after initiation of clozapine therapy, and it is most prominent during sleep, resulting in, among others, wet pillows (Fig. 1) and skin problems.^{2–6} In several case reports, it has also been linked to clinical complications including parotitis, sleeping disorders, and aspiration pneumonia.^{6–8} Moreover, sialorrhea can negatively affect the quality of life and therefore negatively influence medication adherence^{4,9} and as such indirectly lead to psychiatric deterioration.¹⁰

It has been established that sialorrhea is a frequent ADR occurring during clozapine therapy. However, sialorrhea could be overlooked by health care professionals, as this ADR could be overshadowed by the potentially fatal ADRs of clozapine. In this study, we evaluated ADR reporting patterns of sialorrhea in users of clozapine compared with users of other antipsychotics by determining differences in reporting frequency and between health care professionals and consumers.

MATERIALS AND METHODS

Setting

This study was conducted using reports in the World Health Organization (WHO) global Individual Case Safety Report (ICSR) database, VigiBase.¹¹ In 1968, in the aftermath of the thalidomide disaster in the early 1960s, the WHO program for International Drug Monitoring was established. In each country participating in this program, a national center for pharmacovigilance collects and manages suspected ADR case reports. These ICSRs are sent to the Uppsala Monitoring Centre, the WHO Collaborating Centre for International Drug Monitoring, which stores the reports in the WHO global ICSR database, VigiBase. Individual Case Safety Reports in VigiBase include patient demographics, suspected drugs, suspected ADRs, and additional information relevant to the case.¹¹ By May 2016, the VigiBase database contained more than 12 million case reports originating from more than a hundred national pharmacovigilance centers from all over the world. Suspected ADRs are coded at the originating national center, either according to the WHO Adverse Reaction Terminology or the Medical Dictionary for Regulatory Activities (MedDRA). In the current study, the MedDRA hierarchy was used for the evaluation of reported ADRs in the ICSRs.



FIGURE 1. Saliva stains on a pillow as a result of sialorrhoea.

Suspected drugs are classified in Vigibase according to the Anatomical Therapeutic Chemical (ATC) classification.

Study Population

All reports in Vigibase related to clozapine (N05AH02) or other antipsychotics (ATC codes N05A, excluding lithium [N05AN01]) notified since the establishment of Vigibase in 1968 until May 2016 were selected. Causality assessment of the evaluated ADR reports was not performed, meaning reports were included not taking into account the reported level of causality. Reports without a valid MedDRA code were excluded. Duplicate drug-ADR pairs within each unique ICSR report were merged into one record.

Design and Outcome

Drug-ADR pairs involving all antipsychotics were divided into reports involving clozapine or other antipsychotics. To assess the association between involvement of clozapine in comparison with other antipsychotics and sialorrhoea, a case/noncase approach¹² was used among reports with antipsychotics termed as the suspected drug.

Cases were defined as drug-ADR pairs associated with antipsychotic use mentioning the ADR “salivary hypersecretion” (MedDRA code 10039424, preferred term). The noncase group consisted of pairs involving an antipsychotic agent mentioning ADRs other than salivary hypersecretion.

Exposure was defined as the identification of clozapine (N05AH02) being marked as the suspected drug in an ADR report, whereas nonexposure to clozapine was defined as the presence of an antipsychotic agent other than clozapine (ATC codes N05A, excluding lithium [N05AN01]) being marked as the suspected drug in an ADR report.

Report data were stratified by reporter types health care professionals and consumers. Health care professionals included reporter types “physician,” “pharmacist,” “other health professional,” “general practitioner,” and “specialist physician.” Drug-ADR pairs reported by consumers included “consumer/non-health professional” marked as reporter type.

Potential Confounding and Effect-Modifying Variables

Age, sex, reporting year, and reporter type were recorded and explored for potential confounding or effect modification. Age was categorized into 4 categories: <40, 40 to 65, 65 to 80, and 80 years or older. Time periods were categorized in decennia, from

1968 onward. A stratified analysis was performed by reporter types: health care professionals and consumers.

Data Analysis

Characteristics of the cases and controls were analyzed using *t* test and χ^2 tests with respect to the age, sex, reporter type, and time categories. The association between sialorrhoea and presence of each ADR of clozapine was expressed as reporting odds ratios (RORs) as a measure of disproportionality between clozapine and other antipsychotics, accompanied with 95% confidence intervals (CIs). The ROR was based on a 2 × 2 contingency table:

$$ROR = (a/c)/(b/d) = ad/bc$$

in which *a* and *c* denote the cases among the clozapine and other antipsychotic pairs, respectively, and *b* and *d* denote the noncases among clozapine and other antipsychotic pairs, respectively.

The unit of analysis was the drug-ADR pair rather than the unique ICSR report itself.

A multivariate regression analysis was performed to assess confounding and effect modifications (see previous discussion). A variable was termed *confounder* if it independently changed the ROR with more than 10%. All confounders were incorporated into the multivariable model.

RESULTS

By May 2016, Vigibase contained 12,612,671 ICSRs filed, representing a total of 46,894,844 drug-ADR pairs. Antipsychotics were termed as the suspected drug in 1,169,254 drug-ADR pairs (2.49%). Of these 20.8% (n = 243,564) were related to clozapine and 79.2% (n = 925,690) were related to other antipsychotics. Although clozapine-ADR pairs were attributed to male

TABLE 1. Characteristics of Reported Suspected Drug-ADR Pairs

Variable	Clozapine ADRs	Other
	(n = 243,564 [20.8%])	Antipsychotic ADRs (n = 925,690 [79.2%])
Age, mean (SD), y	43.4 (15.4)	44.04 (19.1)
<40 y, n (%)	92,278 (37.9)	293,255 (31.7)
40–65 y, n (%)	100,626 (41.3)	297,704 (32.2)
65–80 y, n (%)	17,375 (7.1)	70,182 (7.6)
>80 y, n (%)	3611 (1.5)	33,793 (3.7)
Unknown, n (%)	29,674 (12.2)	230,756 (24.9)
Sex, n (%)		
Male	148,832 (61.1)	415,289 (44.9)
Female	89,267 (36.7)	462,571 (50.0)
Unknown	5465 (2.2)	47,830 (5.1)
Reporter, n (%)		
Health care professional	146,794 (60.3)	428,869 (46.3)
Consumer	5521 (2.3)	221,145 (23.9)
Other	66,416 (27.3)	135,711 (14.7)
Unknown	24,833 (10.2)	139,965 (15.1)
Reporting year, n (%)		
2010–2016	127,435 (52.3)	586,875 (63.4)
2000–2009	77,712 (31.9)	243,818 (26.3)
1990–1999	37,679 (15.5)	57,929 (6.3)
1980–1989	471 (0.2)	22,887 (2.5)
1970–1979	267 (0.1)	12,523 (1.4)
1968–1969	0 (0.0)	1658 (0.2)

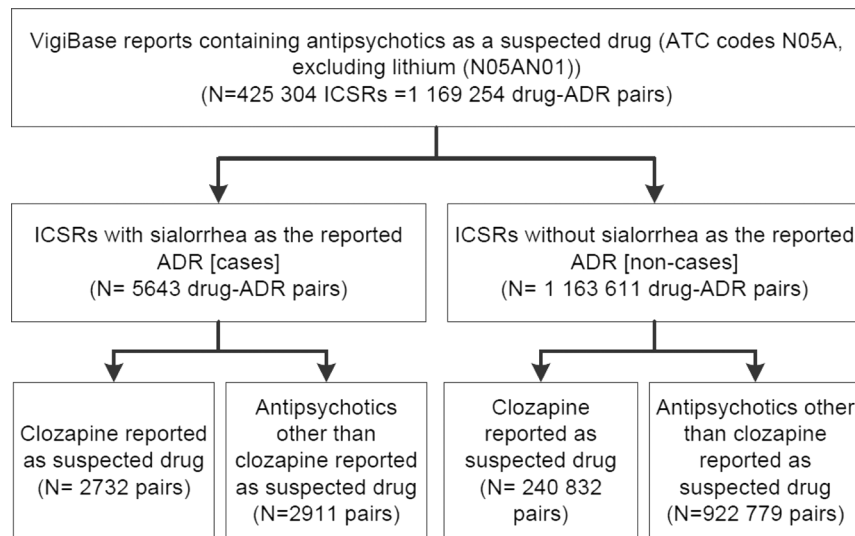


FIGURE 2. The study flow diagram.

individuals (61.1%), a proportion of 50.0% of all other antipsychotic-ADR pairs was attributed to female individuals (Table 1). Health care professionals were the largest contributors of the clozapine-ADR pairs (60.3%), whereas consumers only reported 2.3%.

A total of 5643 (0.48%) drug-ADR pairs were identified as cases and 1,163,611 pairs were noncases. Of all cases, a total of 2732 were attributed to clozapine pairs and a total of 2911 to other antipsychotic pairs (Fig. 2), resulting in sialorrhea being reported nearly 4 times more often (ROR, 3.60 [95% CI, 3.41–3.79]) in users of clozapine than in users of other antipsychotics. From all included variables in the multivariate regression analysis, the variable “reporter type” was identified as a confounder. When stratified by reporter type, sialorrhea was reported by consumers nearly 20 times more often in clozapine compared with other antipsychotics (ROR, 19.8 [95% CI, 15.1–25.9]), whereas this ratio was found nearly 8 times lower in health care professionals (ROR, 2.44 [95% CI, 2.27–2.63]).

DISCUSSION

Sialorrhea is reported nearly 4 times more frequently in reports with clozapine as suspected drug in comparison with other antipsychotics. This relative reporting rate was found 8 times higher in consumers compared with health care professionals (Table 2). From the results of our stratified analysis, we observed a discrepancy in ADR reporting in consumers compared with health care professionals. More specifically, there were more reports on sialorrhea involving clozapine reported by consumers than health care professionals after stratification by reporter type. None of such large discrepancy between these reporter types was found for other antipsychotic agents. This implicates differences in interests and focus of ADR reporting among consumers and health care professionals when it comes to clozapine therapy. From the view of health care professionals, sialorrhea in clozapine therapy seemed to be one of the ADRs that are of less concern compared with life-threatening ADRs including myocarditis and hematological adverse effects. For patients themselves, ADRs impairing activities of daily life and quality of life seem to be relatively more important.

Within the group of antipsychotics, clozapine accounts for nearly half of all reported drug-ADR pairs involving sialorrhea (Table 1). This is a markedly high proportion, certainly because

clozapine is reserved as a drug of last resort, and therefore, overall prescribing rates are expected to be lower than for other antipsychotics.¹³ This high reporting rate may be partially explained by the fact that clozapine is subject to mandatory hematological and serum level monitoring in certain countries, including the United Kingdom and the United States. As a consequence, this could lower the reporting threshold and raise awareness to report clozapine-related ADRs. In addition, US pharmaceutical companies were previously obliged to maintain a clozapine registry as part of a postmarketing drug surveillance program. Postmarketing ADRs were assessed and reported by US manufacturers on behalf of consumers. This could explain why some of the ADRs, including neutropenia, leukocytosis, and eosinophilia (data not shown), labeled as reported by consumers, are unlikely direct reports by consumers, as these require objective professional examination. The adjusted stratum-specific ROR for the reporter type “consumers” should therefore be interpreted with caution.

A strength of our study is the data source that is used. VigiBase is the largest available pharmacovigilance database and therefore enables to perform disproportionality analyses with high statistical power. It also enables to evaluate unexpected or unknown reported ADRs.

Moreover, the disproportionality analysis is a validated method in drug safety research and surveillance.¹⁴

However, several limitations in our study need to be addressed. First and most importantly, data were obtained through spontaneous reporting without additional clinical assessment or

TABLE 2. Stratified Analysis by Reporter Types Health care Professionals and Consumers

	Sialorrhea Reported by Health Care Professionals	Sialorrhea Reported by Consumers	Overall
Clozapine (n of total)	1290/146,794	79/5521	2732/243,564
Other antipsychotic (n of total)	1553/428,869	162/221,145	2911/925,690
ROR (95% CI)	2.44 (2.27–2.63)	19.8 (15.1–25.9)	3.60 (3.41–3.79)

qualitative verifications by the authors. Therefore, the causality of sialorrhea due to exposure to clozapine or any of the other antipsychotic agents cannot be established with full certainty.¹⁵ Although assessment of the quality regarding reports is included in VigiBase, this parameter was not included in our data set. In this context, clinical details such as severity of drooling and clozapine dosage were not included in our analyses. In addition, because of the spontaneous nature of ADR reporting to VigiBase, our findings provide a signal regarding differences in occurrence of sialorrhea and use of different antipsychotics but do not allow for an absolute and relative reporting rate.¹⁵

Second, it should be noted that VigiBase includes two report formats: “International Drug Information System” and the E2B standard. For our stratified analysis, ICSRs with both report formats were included in the estimation of reporter type proportion. In addition, because consumer reports in the International Drug Information System format are marked as “other,” whereas in the E2B format, they are marked as “consumer/non-health professional,” a sensitivity analysis was performed to estimate the proportion of consumer reports by limiting selection to only E2B reports. This did not substantially change the reporting ratios in consumers (ROR, 19.8 [95% CI, 15.1–25.9]) or in health care professionals (ROR, 2.52 [95% CI, 2.32–2.73]).

Third, comedication (such as antisialagogues) was not tested as a potential confounder of effect modifier in the multivariate regression analysis. Such comedication could potentially lead to misclassifying cases as noncases.

Fourth is the Weber effect, in which severe ADRs and ADRs not listed in the summary of product characteristics are relatively more often reported in newer agents.

Lastly, as discussed earlier, clozapine therapy is subject to hematological monitoring programs that are mandatory in certain countries, thereby increasing the number of health care workers and the number of patient visits, potentially reflected in disproportionate higher incidence of reports and indirectly of sialorrhea reports.

Based on spontaneous reports, sialorrhea was reported almost 4 times more frequently in users of clozapine than in users of other antipsychotics. The reporting rate was found 8 times higher in consumers in comparison with health care professionals, providing a signal of underreporting of sialorrhea by health care professionals and a difference in concerns and focus for reporting this adverse event. This study underlines the importance for health care professionals to incorporate sialorrhea as a relevant topic of discussion into the shared decision process with patients when initiating clozapine therapy.

AUTHOR DISCLOSURE INFORMATION

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