Olfactory-related adverse events: An Analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS)

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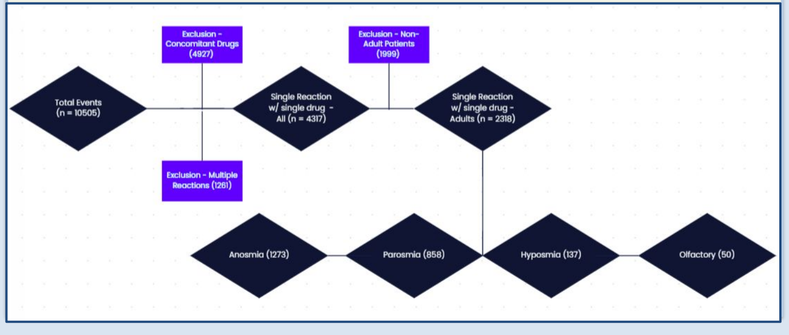
Background

- Olfactory dysfunction encompasses a range of increased, altered, reduced, or complete loss of ability to smell and taste, and has recently gained considerable interest due to its association with the coronavirus pandemic.
- Current literature regarding changes in olfaction are primarily related to neurodegenerative disorders, post-infectious, traumatic sequelae, autoimmune disorders, congenital disorders, and medication side effects.[1]
- > 70 medications with olfactory adverse effects have been identified and ~50% of the top 100 drugs in the U.S. have potential to induce chemosensory adverse effects.[2]
- Other medication-induced olfactory adverse event studies have been performed in the US, but have only been isolated to intranasal medications or oral antibiotics.The following medications were identified.[3,4]
  - Oral Macrolides, Tetracycline, and fluoroquinolones
  - Intranasal corticosteroids, alpha adrenergics, and antihistamines
- An Italian database review identified 182 cases of smell/taste dysfunction.[5]
  - Macrolides (31), terbinafine (17), fluoroquinolones (15), and protein kinase inhibitors (10) were most commonly reported
- *Study objective:* Provide a comprehensive analysis of reported medication induced olfactory-related adverse events (ORAEs) through the FDA Adverse Event Reporting System (FAERS).

Materials and Methods

- *Design*: Retrospective cross-sectional study
- Non-human subject study protocol was reviewed and approved by the Scholarly Activity Review Committee of Mclaren Health Care.
- *Measurements*
  - *Main outcome*: distribution of cases with ORAEs
    - Anosmia, Hyposmia, Olfactory Dysfunction, Parosmia
  - *Main determinant variable*:
    - Suspected product active ingredient (SPAI)
- *Statistical Analysis*
  - Presented in frequencies and percentages
- *Study sample (n = 10505)*
  - ≥ 17 year old patients from any country with reported olfactory-associated adverse events
    - From January 1, 2012 to August 11, 2022
  - Excluded < 17 Year olds, incomplete demographic entries, duplicates
  - Final Study Population (n = 1111)
    - SPAIs with >0.8% of cases per reaction



Results

Table 4. Distribution of cases reported from January 1, 2012 to August 11, 2022, by olfactory-associated adverse reaction, suspected primary active ingredient (N = 10,505 cases reported)

	Olfactory-associated adverse reaction									
	Anosmia N=1273		Hyposnia N=137		Olfactory N=50		Parosmia N=858		All cases reported olfactory related reactions	
Suspected Primary Active Ingredient	n	Percent	n	Percent	n	Percent	n	Percent	n	Percent
Adalimumab	25	1.96%	7	5.11%			26	3.03%	58	5.22%
Apremilast							14	1.63%	14	1.26%
Azithromycin Anhydrous	10	0.79%							10	0.90%
Capecitabine							8	0.93%	8	0.72%
Ciprofloxacin			5	3.65%					5	0.45%
Citalopram Hydrobromide			7	5.11%					7	0.63%
Denosumab							9	1.05%	9	0.81%
Dimethyl Fumarate							21	2.45%	21	1.89%
Duloxetine Hydrochloride							7	0.82%	7	0.63%
Dupilumab	73	5.73%	14	10.22%			23	2.68%	110	9.90%
Etanercept	27	2.12%					27	3.15%	54	4.86%
Etonogestrel							7	0.82%	7	0.63%
Enzalutamide							10	1.17%	10	0.90%
Evolocumab	11	0.86%					11	1.28%	22	1.98%
Fingolimod Hydrochloride	12	0.94%							12	1.08%
Fluticasone Furoate	21	1.65%							21	1.89%
Fluticasone Propionate	115	9.03%	14	10.22%			22	2.56%	151	13.59%
Homeopathics	40	3.14%							40	3.60%
Interferon Beta-1a							9	1.05%	9	0.81%
Lamotrigine			3	2.19%					3	0.27%
Lenalidomide	26	2.04%	3	2.19%			7	0.82%	36	3.24%
Levofloxacin			5	3.65%			9	1.05%	14	1.26%
Levonorgestrel	11	0.86%					20	2.33%	31	2.79%
Levothyroxine Sodium							8	0.93%	8	0.72%
Liraglutide							9	1.05%	9	0.81%
Mometasone Furoate	21	1.65%	7	5.11%					28	2.52%
Moxifloxacin Hydrochloride	12	0.94%							12	1.08%
Ocrelizumab			3	2.19%					3	0.27%
Oxymetazoline	15	1.18%							15	1.35%
Oxymetazoline Hydrochloride	67	5.26%							67	6.03%
Palbociclib	14	1.10%					16	1.86%	30	2.70%
Paroxetine					4	8.00%			4	0.36%
Pregabalin							10	1.17%	10	0.90%
Ramipril							13	1.52%	13	1.17%
Secukinumab	68	5.34%	3	2.19%			8	0.93%	79	7.11%
Semaglutide							11	1.28%	11	0.99%
Sertraline Hydrochloride	13	1.02%					9	1.05%	22	1.98%
Simvastatin							8	0.93%	8	0.72%
Terbinafine	11	0.86%							11	0.99%
Teriparatide							13	1.52%	13	1.17%
Tofacitinib Citrate	28	2.20%					7	0.82%	35	3.15%
Triamcinolone Acetonide	27	2.12%					7	0.82%	34	3.06%
Varenicline Tartrate	13	1.02%					15	1.75%	28	2.52%
Zinc Gluconate	12	0.94%							12	1.08%
Total cases reported									1111	
Total cases per reaction	672		71		4		364			
Percent of cases by reaction	52.8%		51.8 %		8%		42 %			

List in alphabetical order of the suspected active ingredient. Mutually exclusive report

Percentages based on the total of adults with the reaction.

Discussion

- Identified 44 SPAIs in final study population
  - Most Common SPAIs by drug class (n = 1111)
    - Monoclonal Antibodies - 281 (25.29%)
      - Secukinumab (79), Dupilumab (73), Adalimumab (25), Evolocumab (22), Denosumab (9), Ocrelizumab (3)
    - Intranasal Steroid - 234 (21.06%)
      - Fluticasone (172), Triamcinolone (34), Mometasone (28),
    - Immunomodulators -228 (20.52%)
      - Etanercept (54), Lenalidomide (36), Tofacitinib (34), Palbociclib (30), Dimethyl Fumarate (21) Apremilast (14), Fingolimod (12), Enzalutamide (10), Interferons Beta (9), Etonogestrel (7)
    - Intranasal Decongestant (Oxymetazoline) - 82 (7.38%)
    - Antibiotics - 41 (3.69%)
      - Levofloxacin (14), Moxifloxacin (12), Azithromycin (10), Ciprofloxacin (5)
    - Antidepressants - 40 (3.60%)
      - Sertraline (22), Citalopram (7), Duloxetine (7), Paroxetine (4)
    - Various Homeopathics - 40 (3.60%)
- Most Common SPAIs per Reaction Type
  - Anosmia
    - 1) Fluticasone Propionate/Furoate (10.68%)
    - 2) Oxymetazoline Hydrochloride (6.44%)
    - 3) Dupilumab (5.73%)
  - Parosmia
    - 1) Etanercept (3.15%)
    - 2) Adalimumab (3.03%)
    - 3) Dupilumab (2.68%)
  - Hyposmia
    - 1) Dupilumab & Fluticasone Propionate (10.22%)
    - 2) Adalimumab, Citalopram, Mometasone Furoate (5.11%)
    - 3) Ciprofloxacin, Levofloxacin (3.65%)
  - Olfactory
    - 1) Paroxetine (8.00%)
- Olfactory Dysfunction reported more in non-US Countries (54%)
- Conclusion
  - This retrospective cross-sectional analysis identified 44 potential SPAIs which could cause ORAEs.
  - We hope this data will help physicians identify potential causes of ORAEs, and reduce the amount of unnecessary testing and workup
- Limitations.
  - FAERS doesn't list concurrent medications, patient characteristics, comorbidities, or indication of medication use, or receive every adverse event related to a product.
  - It has a risk of duplicate reports or self-reporting bias.
  - Some cases were reported during COVID-19 pandemic, which is associated with olfactory dysfunction.

References and Acknowledgements

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Acknowledgements: We would like to thank the U.S. Food and Drug Administration (FDA) for the idea and collection of the data for this database.The content of this article does not reflect current or future opinion or policy of the U.S. FDA.