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

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Background

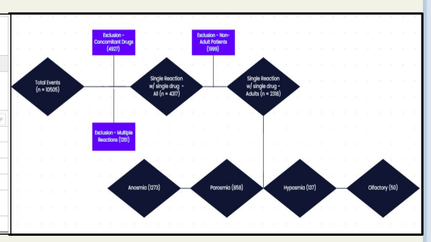
- Olfactory dysfunction encompasses a range of increased, altered, reduced, or complete loss of ability to smell and taste, and has recently gained considerable interest due to its association with the coronavirus pandemic.
- Current literature regarding changes in olfaction are primarily related to 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.[3,4]
- *Study objective:* Provide a comprehensive analysis of reported oral, injectable, and intranasal 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 (OD), Parosmia
  - *Main determinant variable*:
    - Suspected product active ingredient (SPAI)
- *Statistical Analysis*
  - Significance determined by Proportional Reporting Ratio (PPR) >2 or Relative Odds Ratio (ROR) >1 (95% CI)
- *Study sample (n = 10505)*
  - ≥ 17-year-old patients from any country with reported olfactory-associated adverse events
    - January 1, 2012 to August 11, 2022
  - Exclusion: < 17-year-olds, incomplete demographic entries, duplicates
  - Final Study Population (n = 1111)
    - SPAIs with >1% of cases per reaction

Table 3. Descriptive characteristics of adults with olfactory-related adverse events. Data from FDA Adverse Event Reporting System (FAERS), January 1, 2012 to August 11, 2022.

	Olfactory-Related Adverse Event among adults N (%)*			
Characteristics	Anosmia N=1273	Hyposmia N=137	Olfactory Dysfunction N=50	Parosmia N=858
Sex				
Female	841 (66)	76 (55)	33 (66)	594 (69)
Male	418 (33)	59 (43)	17 (34)	262 (31)
Not Specified	14 (1)	2 (1)	-	2 (<1)
Country				
Not United States	516 (41)	49 (36)	27 (54)	282 (33)
United States	757 (59)	88 (64)	23 (46)	576 (67)



Results

Table 4. Suspected Principal Active Ingredient (SPAI) and Reported Anosmia in FAERS.

Suspected Principal Active Ingredient	N	PRR (95% CI)	ROR (95% CI)
Fluticasone propionate	115	1.31 (1.21, 1.42)	2.31† (1.56, 2.71)
Dupilumab	73	1.11 (0.97, 1.25)	1.32 (0.87, 1.74)
Secukinumab	68	1.41 (1.3, 1.52)	3.42†(1.9, 4.01)
Oxymetazoline hydrochloride	67	1.37 (1.25, 1.49)	2.93† (1.67, 3.49)
Homeopathics	40	1.69 (1.64, 1.74)	inf
Tofacitinib citrate	28	1.34 (1.16, 1.51)	2.68† (1.16, 3.52)
Etanercept	27	0.82 (0.55, 1.09)	0.64 (0.37, 1.19)
Triamcinolone acetonide	27	1.07 (0.83, 1.3)	1.18 (0.62, 1.83)
Lenalidomide	26	1.2 (0.99, 1.41)	1.73 (0.82, 2.47)
Adalimumab	25	0.70 (0.40, 1.00)	0.48 (0.28, 1.01)
Fluticasone furoate	21	1.67 (1.63, 1.72)	inf
Mometasone furoate	21	1.25 (1.03, 1.47)	1.99 (0.84, 2.85)
Oxymetazoline	15	1.67 (1.62, 1.72)	inf
Palbociclib	14	1.67 (1.62, 1.72)	inf
Sertraline hydrochloride	13	1.02 (0.68, 1.36)	1.06 (0.44, 1.95)
Varenicline tartrate	13	1.67 (1.62, 1.71)	inf
Fingolimod hydrochloride	12	1.67 (1.62, 1.71)	inf
Moxifloxacin hydrochloride	12	1.67 (1.62, 1.71)	inf
Zinc gluconate	12	1.67 (1.62, 1.71)	inf
Evolocumab	11	0.82 (0.4, 1.24)	0.65 (0.28, 1.49)
Levonorgestrel	11	0.58 (0.1, 1.06)	0.35 (0.17, 1.09)
Terbinafine	11	0.75 (0.32, 1.19)	0.55 (0.24, 1.36)
Azithromycin anhydrous	10	1.66 (1.62, 1.71)	inf

Table 5. Suspected Principal Active Ingredient (SPAI) and Reported Hyposmia in FAERS.

Suspected Product Active Ingredient	N	PRR (95% CI)	ROR (95% CI)
Dupilumab	14	2.24* (1.68, 2.79)	2.42† (1.3, 3.04)
Fluticasone propionate	14	1.56 (1, 2.12)	1.62 (0.88, 2.23)
Adalimumab	7	1.99 (1.25, 2.72)	2.12† (0.93, 2.95)
Citalopram hydrobromide	7	17.25* (17.01, 17.49)	inf
Mometasone furoate	7	4.23* (3.55, 4.91)	5.31† (2.18, 6.2)
Ciprofloxacin	5	16.76* (16.52, 16.99)	inf
Levofloxacin	5	5.94* (5.2, 6.68)	8.68† (2.83, 9.8)
Lamotrigine	3	16.29* (16.06, 16.52)	inf
Lenalidomide	3	1.32 (0.21, 2.42)	1.35 (0.4, 2.55)
Secukinumab	3	0.55 (0.18, 1.69)	0.54 (0.17, 1.72)

Table 6. Suspected Principal Active Ingredient (SPAI) and Reported Parosmia in FAERS.

Suspected Product Active ingredient	N	PRR (95% CI)	ROR (95% CI)
Etanercept	27	1.57 (1.29, 1.85)	2.14† (1.23, 2.69)
Adalimumab	26	1.4 (1.1, 1.7)	1.72† (1.01, 2.25)
Dupilumab	23	0.61 (0.24, 0.99)	0.51 (0.32, 0.99)
Fluticasone propionate	22	0.41 (0.01, 0.8)	0.31 (0.19, 0.78)
Dimethyl fumarate	21	3.18* (3.09, 3.27)	inf
Levonorgestrel	20	2.03* (1.75, 2.3)	3.89† (1.84, 4.64)
Oxymetazoline hydrochloride	16	0.57 (0.12, 1.02)	0.47 (0.27, 1.03)
Triamcinolone acetonide	15	1.09 (0.68, 1.51)	1.15 (0.6, 1.79)
Apremilast	14	3.13* (3.05, 3.22)	inf
Pregabalin	13	2.38* (2.11, 2.66)	6.88† (2.23, 8.01)
Terbinafine	13	1.68 (1.3, 2.06)	2.48† (1.1, 3.29)
Evolocumab	11	1.54 (1.12, 1.97)	2.08 (0.9, 2.93)
Secukinumab	11	0.39 (0.22, 0.95)	0.3 (0.16, 0.94)
Enzalutamide	10	3.11* (3.02, 3.2)	inf
Paroxetine	10	3.11* (3.02, 3.2)	inf
Denosumab	9	3.1* (3.02, 3.19)	inf
Interferon beta-1a	9	3.1* (3.02, 3.19)	inf
Levofloxacin	9	1.99* (1.59, 2.39)	3.76† (1.25, 4.86)
Liraglutide	9	3.1* (3.02, 3.19)	inf
Semaglutide	9	3.1* (3.02, 3.19)	inf
Capecitabine	8	3.1* (3.01, 3.18)	inf
Levothyroxine sodium	8	3.1* (3.01, 3.18)	inf
Ramipril	8	3.1* (3.01, 3.18)	inf
Sertraline hydrochloride	8	1.17 (0.61, 1.72)	1.27 (0.52, 2.16)
Duloxetine hydrochloride	7	3.09* (3.01, 3.18)	inf
Etonogestrel	7	3.09* (3.01, 3.18)	inf
Lenalidomide	7	0.59 (0.3, 1.26)	0.49 (0.21, 1.32)
Teriparatide	7	3.09* (3.01, 3.18)	inf
Tofacitinib citrate	7	0.6 (0.31, 1.27)	0.5 (0.22, 1.34)

Abbreviations:
CI, confidence interval; FAERS, Food and Drug Administration Adverse Event Reporting System; PRR, proportional reporting ratio. ROR, reporting odds ratio; NL, Adverse event not listed under top 300 adverse events for drug name sorted by PRR; Inf: Infinity.
*Indicates signal if PRR≥2. † Indicates signal if the lower limit of the 95% CI for ROR>1.

Results

- Out of 44 SPAIs identified in final study population (n = 1111), the MC reported drugs:
  - Monoclonal Antibodies: 281 (25.29%)
  - Intranasal Steroid: 234 (21.06%)
  - Immunomodulators: 228 (20.52%)
  - Intranasal Decongestant (Oxymetazoline): 82 (7.38%)
  - Antibiotics: 41 (3.69%)
  - Various Homeopathics: 40 (3.60%)
- Significant SPAIs per Reaction
  - Anosmia (4)
    - Fluticasone Propionate
    - Oxymetazoline Hydrochloride
    - Secukinumab
    - Tofacitinib Citrate
  - Hyposmia (6)
    - Citalopram
    - Ciprofloxacin/Levofloxacin
    - Dupilumab
    - Lamotrigine
    - Mometasone Furoate
  - Parosmia (21)
    - Apremilast, Adalimumab, Capecitabine
    - Denosumab, Dimethyl Fumarate, Duloxetine
    - Etanercept, Etonogestrel, Enzalutamide,
    - INF-B, Levofloxacin, Levonorgestrel, Levothyroxine, Liraglutide
    - Pregabalin, Paroxetine, Ramipril, Semaglutide
    - Terbinafine, Teriparatide
  - Olfactory Dysfunction (0)
  - Olfactory Dysfunction reported more in non-US Countries (54%)

Conclusion

- Identified 44 potential SPAIs which could cause ORAEs.
  - 30 Statistically Significant SPAIs
    - Anosmia (4), Hyposmia (5), Parosmia (21), Olfactory Dysfunction (0)
- We hope this data will assist physicians in identification of potential pharmacological causes of olfactory dysfunction.
- Potentially reduce direct healthcare costs by reducing unnecessary testing and workup.
- Limitations:
  - FAERS does not list concurrent medications, patient characteristics, comorbidities, or indication of medication use, or receive every adverse event related to a product.
  - There's 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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