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'Inactive' ingredients in oral medications

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Supplementary Materials:

Materials and Methods

Analysis of piece weights of medications

We extracted a list of available dosages of the top 18 most prescribed active ingredients. (22) Oral solid dosage forms were selected according to availability through the Brigham and Women's Hospital (BWH, Boston, MA) pharmacy. The final dataset consisted of 54 unique medications (Table S1). Data regarding the active ingredient content in these medications was manually curated from Pillbox (<https://pillbox.nlm.nih.gov>), DailyMed (<https://dailymed.nlm.nih.gov/>), as well as directly *via* the web resources of the manufacturers. Dosage was converted for salt forms to ensure that actual mass of included active ingredient was considered in subsequent calculations. Medications were individually unpacked and immediately weighed to reduce impact of humidity absorption. Oral solids were individually weighed in triplicates on an APX-60 scale. The heaviest and lightest agents were re-measured on a Mettler Toledo scale to ensure reproducibility. A total of seven medications were included that shared the same active ingredient and dose compared to another medication in our list to investigate variability between producers and from production by the same manufacturer. Data analysis was performed in Microsoft Excel (Version 2013). To enhance the scope of this analysis, we also manually extracted data from the German provider "Gelbe Liste" (www.gelbe-liste.de; accessed April 10, 2018) which lists piece weights of medications among their active ingredient mass. Manual curation of this data led to a larger dataset of 1,902 medication weights and their active ingredient mass. This dataset was subsequently analyzed in Python (version 2.7.6) to extract percentage of mass of every medication corresponding to the mass of the inactive ingredients. Data was used with permission by "Gelbe Liste" (personal communication Ellen Reifferscheid).

Formulation Data

The NIH Pillbox database (version 201605, <https://pillbox.nlm.nih.gov>) was downloaded in CSV format. Data was processed in KNIME (version 3.2) and Python (version 2.7.6). For data curation, we removed brackets, transformed ingredient names into lowercase, removed special characters (dots, commas, ampersands), unified indications of numbering in names (e.g. "#", "No."), and removed duplicated, trailing, and leading spaces. Furthermore, commonly occurring misspellings or alternative spellings were corrected (see Supplementary Table 8) and commonly occurring differences in word orders were standardized. Through this curation, we reduced the size of the database from 2,504 inactive ingredient entries to 1,154 unique entries (Figure S1). The inactive ingredient portion within a medication was defined as a unique combination of the different inactive ingredients, irrespective of their position in the ingredient list. Following this definition, a total number of 13,287 unique formulations were identified. Similar processing was applied to the active ingredients of medications, resulting in a total of 2,239 unique active ingredients, where an active ingredient is one or a combination of different active pharmaceutical ingredients (APIs). Data on the most commonly prescribed drugs was extracted from 2017 data from the IMS Institute. Data on commonly used GI medications were manually extracted for proton pump inhibitors, histamine 2 receptor blockers and treatments for irritable bowel syndrome (Figure 4).

Identification of Inactive Ingredients as Allergens and Irritants

Raw counts of all PubMed entries for "excipient allergy" and "excipient irritation" were retrieved from the PubMed website (accessed on May 25, 2018) and exported into Prism for plotting.

Reports of inactive ingredients were identified from Pubmed (<https://www.ncbi.nlm.nih.gov/pubmed/>, accessed on August 16, 2017) by querying for reviews published in the past 25 years in English. The search terms looked for reviews with all permutations of the search terms “excipient” or “inactive ingredient” combined with either “allergy”, “adverse reaction”, or “reaction”. 128 unique articles were initially reviewed (Table S3). Abstracts and titles were reviewed to exclude studies that were focused on injectable or topical medications, were not discussing inactive ingredients, were written in a language other than English, or were otherwise out of scope for this study. 20 papers were ultimately included and lead to the identification of 38 inactive ingredients that have previously been reported to lead to classic allergic reactions in patients.

Statistical analysis and plotting

Data was analyzed in Python (version 2.7.6) using the Numpy (www.numpy.org) and SciPy (www.scipy.org) libraries. Networks were generated in Gephi (version 0.9.2; www.gephi.org) using the Yifan Hu layout algorithm with standard parameters. Survey data was visualized using SankeyMatic (www.sankeymatic.com). Other plots were generated using matplotlib (www.matplotlib.org). All plots were processed in Inkscape (version 0.91). Statistical tests and statistical analysis was performed in Python (version 2.7.6).



Fig S1. **A** Summary statistics for different allergen classes of potential allergens. Pie charts showcase the percentage of drugs where all formulations contain at least one allergen from the allergen ingredient classes (food, polymers, dyes, sugars, others), dark gray corresponds to drugs where all available medications are free of such potentially allergy-inducing inactive ingredients belonging to those classes, while light gray highlights drugs where some but not all formulations contain at least one ingredient from these classes. **B** Overall potential allergen content in different formulations of active ingredients. A total of 72% of APIs have all their medications contain at least one of these allergy-associated inactive ingredients (black bar). Only medications for 12% of APIs are completely free of concerning inactive ingredients (dark grey bar), while 16% of APIs have medications for which at least one allergen-free formulation exists (light grey bar).

2504
 ↓ remove brackets
 2256
 ↓ lowercase
 1438
 ↓ remove special characters
 1419
 ↓ unify numbering
 1378
 ↓ remove spaces
 1241
 ↓ remove typos and unify word orders
 1154

Fig. S2. Flow-chart visualizing data curation strategy for Pillbox extraction. Numbers refer to the number of unique inactive ingredients names that can be in the database after every curation step. Through this curation, we reduced the number of inactive ingredients in the Pillbox database to 1154 (46% of original database) by removing 1350 alternative spellings and misspellings.

Table S1. Piece weight analysis of different versions of most commonly prescribed medications.

Active ingredient	Dose	Producer	Weight 1	Weight 2	Weight 3	% Inactive
amlodipine	2.5mg	Major Pharma	49.3	49.0	48.9	92.93%
	5mg	AvKARE/AvPA K	202.1	202.0	202.2	96.57%
	10mg	McKesson	203.9	203.7	203.6	93.19%
amoxicillin	250mg	NorthStar Rx	379.2	379.0	379.1	34.05%
	500mg	NorthStar Rx	717.0	717.3	716.5	30.26%
Atorvastatin	20mg	AvKARE/AvPA K	206.4	206.0	206.1	89.50%
	80mg	Major Pharma	856.3	857.0	856.7	89.89%
azithromycin	250mg	American Health Packaging	463.3	463.2	462.8	44.72%
	600mg	Teva	1052.4	1052.3	1052.3	41.61%
furosemide	20mg	West Ward	85.3	85.5	85.4	76.58%
	40mg	West Ward	168.6	168.2	168.6	76.26%
	80mg	West Ward	339.8	339.7	339.6	76.45%
gabapentin	100mg	McKesson	177.2	176.8	177.2	43.52%
	300mg	McKesson	462.3	462.4	462.3	35.11%

	400mg	McKesson	610.1	610.3	609.8	34.43%
hydrochlorothiazide	25mg	McKesson	110.5	110.7	110.5	77.39%
ibuprofen	200mg	LNK	327.1	326.6	326.8	38.81%
	400mg	McKesson	567.3	566.8	567.2	29.47%
	600mg	McKesson	867.7	867.9	867.9	30.86%
	800mg	McKesson	1179.8	1179.4	1179.6	32.18%
levothyroxine	25mcg	Mylan Inst	130.2	129.7	130.0	99.98%
	50mcg	Mylan Inst	129.0	128.8	128.9	99.96%
	75mcg	Mylan Inst	130.1	129.6	130.0	99.94%
	88mcg	Mylan Inst	131.2	130.8	131.0	99.93%
	100mcg	Mylan Inst	128.6	128.7	128.4	99.92%
	112mcg	Mylan Inst	130.6	130.5	130.2	99.91%
	125mcg	Mylan Inst	129.8	129.5	129.6	99.90%
	125mcg	AbbVie	128.9	130.2	129.6	99.90%
	125mcg	AbbVie	131.1	131.2	130.7	99.90%
	137mcg	Mylan Inst	128.8	128.8	129.2	99.89%
	150mcg	Mylan Inst	130.1	130.0	129.9	99.88%
	200mcg	AbbVie	132.3	131.9	131.7	99.85%
lisinopril	2.5mg	Qualitest	97.0	96.9	96.6	97.42%
	5mg	Major Pharma	106.9	106.8	106.7	95.32%
	10mg	Major Pharma	213.6	213.9	213.6	95.32%
	20mg	McKesson	194.9	194.6	194.7	89.73%
	20mg	McKesson	195.8	195.9	196.4	89.80%
losartan	25mg	McKesson	92.3	92.4	92.2	72.91%
	50mg	McKesson	182.9	183.2	182.8	72.67%
metformin	500mg	McKesson	602.6	602.1	602.5	17.00%
	850mg	Major Pharma	961.6	961.6	961.8	11.61%
metoprolol tartrate	25mg	American Health Packaging	146.9	146.7	146.3	83.75%
	50mg	American Health Packaging	291.7	292.0	291.7	83.67%
	50mg	American Health Packaging	292.8	292.2	292.9	83.71%
	100mg	American Health Packaging	482.6	484.4	482.3	80.27%
metoprolol succinate	25mg	Major Pharma	102.3	102.3	102.0	75.54%
	50mg	Major Pharma	205.5	205.1	205.9	75.67%
omeprazole	20mg	Major Pharma	309.9	310.1	309.7	93.55%
sertraline	25mg	American Health Packaging	78.2	78.1	77.6	64.16%

	50mg	American Health Packaging	153.8	153.7	153.4	63.63%
	100mg	American Health Packaging	307.6	307.7	307.8	63.68%
simvastatin	5mg	McKesson	49.9	49.9	50.0	89.99%
	10mg	McKesson	100.8	100.8	100.3	90.06%
	20mg	McKesson	204.2	203.9	204.2	90.20%

Table S2. Top ten most common inactive ingredients in Pillbox.

Inactive ingredient	Number of occurrence in Pillbox (total 42,052)
magnesium stearate	30263 (72%)
microcrystalline cellulose	23325 (55%)
titanium dioxide	21125 (50%)
silicon dioxide	15612 (37%)
starch corn	15405 (37%)
lactose monohydrate	11658 (28%)
hypromelloses	11547 (27%)
talc	10472 (25%)
croscarmellose sodium	8760 (21%)
polyethylene glycols	8282 (20%)

Table S3. List of publications analyzed for identification of reports of allergic reactions or gastrointestinal side effects through inactive ingredients in medications.

PMID	Included?	Extracted inactive ingredients or reason to exclude
28684647	Yes	Parabens and benzoates
28613520	No	not relevant
28163222	No	not relevant
27882527	No	not relevant
27834127	Yes	Carboxymethylcellulose (CMC), povidones, PEG (macrogols), sulfites, benzyl alcohol, and tweens
27712572	Yes	Polyethylene glycol (PEG)
27534768	No	Inhaled medications
28827390	Yes	wheat starch, peanut oil/arachis oil, benzyl alcohol
27491381	No	not relevant
27436328	No	not relevant
27196817	Yes	PEG, polysorbates (Tweens), poloxamers, PEG castor oils, laureth-9, cetomacrogol, PEG 40 stearate, cetomacrogol 1000, PEG 6000, polysorbate 80, hydroxyethylated starch, poloxamer, polysorbate 80

27128715	No	environmental
26636421	No	not relevant
26419538	No	topical medications
26211812	Yes	succinate esters, carboxymethylcellulose (CMC), polyethylene glycol (PEG; macrogol), lactose
26156542	No	topical medications
25885102	No	topical medications
25764151	No	Inhaled medications
25751935	No	injections
25514481	No	Nasal and respiratory delivery only
25384223	No	Topical drugs
25341165	No	only IV route
25017684	Yes	Carboxymethylcellulose (also called carmellose or croscarmellose, sodium carboxymethylcellulose, and E466), tartrazine, FD&C Blue No. 1 (bright blue), Blue No. 2 (indigo carmine), orange disperse 3 (Sunset Yellow), Povidone (PVP, polyvinylpyrrolidone), Sodium benzoate (E211), sulfites
25017683	No	Topical drugs
24878443	Yes	gelatin, milk, casein, lactose, lactulose
24832168	No	Topical drugs
24714850	No	IV drugs
24674688	No	IV drugs
24656778	No	Topical drugs
24565702	No	not relevant
24559657	No	not relevant
24456019	No	Topical drugs
24173385	No	no adverse effects reported
24051350	No	IV
24002150	No	Topical drugs
23765411	No	no inactive ingredients discussed
23730887	No	All IV or SC formulations
23544966	No	Inhaled medications
23543606	No	no adverse effects reported
23504430	No	not relevant
23340678	No	not relevant
23339763	No	not relevant
23292495	No	IV
25674402	No	focus on delivery properties instead of adverse reactions
23243989	No	japanese article
23238161	No	Injections
22833905	No	no focus on adverse events
22707362	No	focus on stability instead of adverse events
22394125	No	Topical drug

22312932	Yes	casein, lactose, banana essence, vanilla, vanillin
24300191	No	ophthalmic products
22099411	No	french article
21801484	No	not relevant
21787819	No	nanomediciines
21741802	No	treatment
21626047	No	nutritional supplements
21611683	No	topical
21199198	No	Inhaled medications
20949699	No	sc injection
20861601	No	Parenteral
20517534	No	Parenteral
20185893	No	Topical drug
20128230	Yes	Carboxymethylcellulose (also called CMC, carmelose)
20013666	No	Otic drops
19732201	Yes	indigo carmine (E132), Sunset yellow, Quinoline yellow
19580371	Yes	corn syrup, Benzalkonium chloride, Allura red (E129; FD&C Red No 40), Brilliant blue (E133; FD&C Blue No 1), Erythrosine (E127; FD&C Red No 3), Indigo carmine (E132; FD&C Blue No 2), Sunset yellow (E110; FD&C Yellow No 6), Tartrazine (E102; FD&C Yellow No 5)
19567843	Yes	methylhydroxybenzoate, propylhydroxybenzoate, cetyl alcohol, stearyl alcohol, polysorbate 80, arachis oil
19467048	No	Topical dental
19240542	No	Topical/ocular drugs
18845195	No	Topical/ocular drugs
18830864	No	generally topical
18497245	No	German, topical
17159596	No	Parenteral
17037081	No	preserving transplants
17017934	No	ophthalmic products
16960822	No	Focused on chemical reactions
16868222	No	comparing opioid formulations
16792601	No	discussion of allergen tolerance
16572992	No	Chinese
16303277	No	discussion of terms, not the products
16180936	No	discussion of terms, not the products
16018907	No	Ingredient discussed is only used in parenterals; it isn't in pillbox
15996453	No	Parenteral
15788144	No	Topical sunscreens
15778049	No	Focused on chemical reactions
15714807	No	Chinese
14977910	No	Parenteral

13679965	No	Spanish
12964493	Yes	amaranth, benzalkonium chloride, sunset yellow, parabens, peanut oil, ponceau, sulfites, tartrazine, brilliant black BN (E151), carmoisine (E122, azorubine), Bronopol, Castor Oil, Corn starch, mercury, Sesame Oil, Soybean oil
12871181	Yes	carboxymethylcellulose
12721396	No	Parenteral, focus on actives
12614517	No	Topical, focus on microbicides
12042063	No	Topical/ocular drugs
11392448	No	Parenteral
11392447	No	Parenteral
11361009	No	Focused on chemical reactions
11325479	No	Focused on chemical reactions
11135703	No	Parenteral
10502611	No	Focused on pharmaceutical properties
10229638	No	Focused on breakdown of protein/peptide products
9057785	Yes	Diethylene glycol
9024461	Yes	sulfur dioxide, sodium sulfite, sodium bisulfite, potassium bisulfite, sodium metabisulfite, and potassium metabisulfite, Aspartame, Saccharin, tartrazine (FD&C Yellow No. 5), sunset yellow, new coccine, amaranth, erythrosine, indigo carmine (FD&C Blue No. 2), ponceau, Brilliant Blue (FD&C Blue No. 1), methyl blue, quinolone yellow, FD&C Red No. 40, lactose, propylene glycol, Benzalkonium chloride, Allura red (E129; FD&C Red No 40), Brilliant blue (E133; FD&C Blue No 1), Erythrosine (E127; FD&C Red No 3), Indigo carmine (E132; FD&C Blue No 2), Sunset yellow (E110; FD&C Yellow No 6), Tartrazine (E102; FD&C Yellow No 5)
8877241	Yes	FD&C yellow #5 (tartrazine), FD&C yellow #6 (sunset yellow), FD&C Blue #1, FD&C Blue #2, carmine color, methylparaben, propylparaben, aspartame, mannitol, sucrose
8766194	No	Inhaled medications
8644576	No	Topical/ocular drugs
8729891	No	Parenteral
8571282	No	French
7600718	No	Topical sunscreens
8535931	Yes	carboxymethylcellulose, sulfur dioxide, Tartrazine (yellow dye No. 5, E 102), ponceau, erythrosine, Benzoic acid, Aminobenzoic acid, para-hydroxybenzoic acid (parabens)
7551218	No	Used for injected medications
7842686	No	Topical meds
8378865	No	German
7912532	No	taxol is parenteral
1421646	No	Reaction to katerolac, an active ingredient

1497796	No	parenteral/sc
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Table S4. Lactose content of various medications.

Drug	Lactose content [mg]	Pubmed ID
Amlodipine	140.00-151.00	24732384
Bisoprolol	1.26-136.00	24732384
Enalapril	78.00-253.60	24732384
Clozapine	32.44-281.62	24732384
Loratadine	62.50-75.00	24732384
Nevirapine	168.00-464.00	24732384
Simvastatin	35.00-576.24	24732384
Capecitabine	7.00-68.95	24732384
Fluconazole	16.60-210.00	24732384
Levofloxacin	3.60-26.45	24732384
Losartan	4.50-231.60	24732384
Azathioprine	34.36-116.00	24732384
Allopurinol	57.00-171.00	24732384
Merbentyl 10mg	74.00	19035974
Pro-banthine 15mg	38.00	19035974
Colofac 135mg	95.00	19035974
Mebeverine hydrochloride 135mg	99.00	19035974
Codeine phosphate 30mg	46.00	19035974
Imodium 2mg	125.00	19035974
Imodium 2mg	108.00	19035974
Losec 40mg	4.00	19035974
Zoton Fastab 30mg	28.00	19035974
Domperidone 10mg	56.00	19035974
Metoclopramide 10mg	71.00	19035974
Prochlorperazine 5mg	70.00	19035974
Valupak multivitamins	38.00	19035974
Merbentyl 10mg	74.00	19035974
Pro-banthine 15mg	38.00	19035974
Colofac 135mg	95.00	19035974
Mebeverine hydrochloride 135mg	99.00	19035974
Codeine phosphate 30mg	46.00	19035974
Imodium 2mg	125.00	19035974
Imodium 2mg	108.00	19035974
Picolax	4.00	19035974
Senokot 7.5mg	16.00	19035974

Celevac 500mg	27.70	19035974
Dulco-Lax 5mg	41.00	19035974
Destolit 150mg	78.00	19035974
Pancrex V tablets	54.00	19035974
Amitryptiline 10mg	43.00	19035974
Allegron 10mg	38.00	19035974
Citalopram 20mg	45.00	19035974
OxyContin 10mg	69.25	21766071
OxyContin 20mg	59.25	21766071
OxyContin 40mg	32.25	21766071
OxyContin 80mg	78.50	21766071
Morphine 10mg	90.00	21766071
Morphine 30mg	70.00	21766071

Table S5: - Corrected and identified misspellings or alternative spellings in the Pillbox database.

<u>Ingredient name</u>	<u>Identified misspellings or alternative spellings</u>
sulfate	sulphate
glycolate	glycollate
stearyl	steryl
dioxide	dioxde
triacetin	tracetin
tricalcium phosphate	tribasic calcium phosphate
dihydrate	dehydrate
gallate	gallette
pregelatinized	pregenatinized, pregelatinzed, pregelatinised, pregalatinized, pregelitanized

povidone	povidine
polyethylene	polyehtylene
polydextrose	polydestrose
polacrilin	polacrillin
grandiflorus	grandiflorum
oleic	olealic
microcrystalline	mircocrystalline, mircrocristalline, microcrystalline, micro-crystalline
parabens	paraben
copolymer	co-polymer
stearate	sterate, strearate, searate
macrogol	macrogel
oxide	oxides
methylcellulose	methylcellulose, methyl cellulose, methycellulose
monohydrate	mohydrate, mohydrte, monhydrate
hydroxypropyl	hydroxypropl, hydroxipropyl, hydroxy propyl
vegetable	vegtable
ethylcelluloses	ethylcellulose, ethyl-cellulose
croscarmellose	croscramellose

crospovidone crospovidine, crospovidone

corn starch cornstarch

colloidal collidiol, colloidial, collodial, colloidal, collidiol, colloidol

silicon silicone, solicon, sillicon

carboxymethylcellulose carboxymethyl cellulose

aluminium aluminum, alumina

alpha-lipoic alpha lipoic

anhydrous anhdrous, anyhydrous

acetaminophen acetamiphen

monooleate mooleate

croscarmellose crosscarmellose