

Original Research Article

Polyallergy (Multiple Chemical Sensitivity) is Associated with Excessive Healthcare Utilization, Greater Psychotropic Use, and Greater Mental Health/Functional Somatic Syndrome Disorder Diagnoses: A Large Cohort Retrospective Study

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Objective: Associations between the crude capture of polyallergy—also known as multiple chemical sensitivity or multiple drug intolerance syndrome—and mental health/functional somatic syndrome disorders, healthcare utilization, or other clinical phenomenon have not been examined extensively. **Methods:** An IRB-approved retrospective chart review of all patients between age 18 and 70 who had a clinical encounter at a large medical center between 2009 and 2014. Patients were stratified into 4 categories based on the absolute number of chart-documented allergies: (1) no allergies; (2) normal allergy (1–4 allergies); (3) polyallergy (5–9 allergies); and (4) “ultrapolyallergy,” (≥ 10 allergies), which were corroborated through a sensitivity analysis. Demographics, comorbidities, and medications were clustered per allergy grouping. Analysis of variance, chi-square, and multivariable logistic regression analyses were employed to test for associations.

Results: 2,007,434 patients were examined

Key words: multiple drug intolerance syndrome, multiple chemical sensitivity, anxiety, polyallergy, central sensitization.

(“no allergy” group, $n = 1,423,631$, 70.9%; “normal allergy” group: $n = 549,927$, 27.4%; “polyallergy” group $n = 29,453$, 1.5%; “ultrapolyallergy” group, $n = 4,423$, 0.22%). Proportion of females increased from 51% in the “no allergy” group to 89.6% in the “ultrapolyallergy” group ($p < 0.001$). Rates of mental health and functional somatic syndrome disorder diagnoses increased significantly across allergy groups ($p < 0.001$). All psychotropic medication classes were increased significantly across allergy groups ($p < 0.001$). Healthcare utilization was also significantly elevated across allergy cohorts ($p < 0.001$).

Conclusions: This study demonstrates that polyallergy/multiple chemical sensitivity may serve as a crude yet meaningful indicator of comorbid psychopathology. Drug intolerance mechanisms are reviewed, and both clinical and investigational implications are examined.

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Polyallergy (Multiple Chemical Sensitivity) is Associated

INTRODUCTION

Patient-reported adverse medication reactions are routinely documented by clinicians in medical records as “allergies” despite at times a lack of confirmation of immune-mediated mechanisms. High numbers of such adverse reactions may complicate clinical care, as clinicians are often uncertain of the safety or suitability of particular agents when previously listed as “allergies.” Patients with multiple documented adverse medication reactions lacking such physiological explanation have been described variably as demonstrating either multiple chemical sensitivity (MCS),¹ multiple drug intolerance syndrome (MDIS),² or “polyallergy.”³ These characterizations utilize different definitions, but all have been studied in terms of epidemiology, typical features, and comorbidities. MCS, for instance, has been defined as a chronic condition with symptoms in multiple organ systems that recur reproducibly in response to low levels of exposure to multiple unrelated chemicals which improve or resolve when incitants are removed¹; over time, however, the condition has been associated with numerous other functional somatic syndrome disorders, such as fibromyalgia and chronic fatigue syndrome.^{4,5} MDIS, alternatively, is defined simply as intolerance to 3 or more unrelated medications² and has been associated with anxiety,⁶ somatization,⁷ poor emotional expression,⁸ and high healthcare utilization.^{2,9} Still other

authors have defined “polyallergy” as the presence of any 4 or more documented drug adverse reactions, regardless if the medications are related or not.³ The association between the absolute number of patient-reported allergies and specific clinical markers of interests has been demonstrated in limited studies. For instance, Park et al.³ found a correlation between the number of allergies reported and the likelihood that a patient's seizure events were nonepileptic (psychogenic) as opposed to epileptic. Specifically, those with video-electroencephalographic evidence of psychogenic nonepileptic seizures (PNES) showed a statistically-significant higher number of reported and documented allergies as compared to patients with epilepsy.³ A second study similarly noted that patients with PNES averaged statistically-significant greater numbers of self-reported allergies than patients with epilepsy, and that each additional allergy linearly increased the likelihood of patients having PNES over epilepsy by 3%.¹⁰ Given these recent studies and the broader range captured by the term, “polyallergy” will be used hereafter to represent multiple reported adverse drug reactions, MDIS, and/or MCS.

Correlations have not been extended to other conditions, health care utilization patterns, or other clinical phenomenon. As elevated health care utilization has been linked to various functional somatic syndromes (including conversion disorder/PNES), the phenomenon of polyallergy warrants further examination in groups

TABLE 1. Demographic Summary by Allergy Category

Factor	No allergies (<i>n</i> = 1,423,631)		“Normal” allergies (1–4 allergies) (<i>n</i> = 549,927)		“Polyallergy” (5–9 allergies) (<i>n</i> = 29,453)		“Ultrapolyallergy” (>9 allergies) (<i>n</i> = 4423)		<i>p</i> value
	<i>n</i>	<i>n</i> (%)	<i>n</i>	<i>n</i> (%)	<i>n</i>	<i>n</i> (%)	<i>n</i>	<i>n</i> (%)	
Age	1,423,631	44.3 ± 14.7	549,927	47.0 ± 14.4	29,453	50.4 ± 13.5	4423	52.4 ± 13.0	<0.001*
Gender	1,423,534		549,922		29,452		4423		<0.001†
Female		726,648 (51.0)		353,010 (64.2)		24,340 (82.6)		3965 (89.6)	
Male		696,886 (49.0)		196,912 (35.8)		5112 (17.4)		458 (10.4)	
Marital status	1,370,514		540,158		28,966		4356		<0.001†
Married		672,717 (49.1)		285,825 (52.9)		15,560 (53.7)		2320 (53.3)	
Single		590,372 (43.1)		196,636 (36.4)		8926 (30.8)		1240 (28.5)	
Divorced		79,626 (5.8)		41,650 (7.7)		3197 (11.0)		538 (12.4)	
Widowed		16,052 (1.2)		10,091 (1.9)		868 (3.0)		194 (4.5)	
Legally separated		10,391 (0.76)		5359 (0.99)		379 (1.3)		59 (1.4)	
Domestic partner		932 (0.07)		467 (0.09)		25 (0.09)		4(0.09)	
Other		424 (0.03)		130 (0.02)		11 (0.04)		1(0.02)	

Values presented as Mean ± SD or *n* (column %). *p* values:

* ANOVA,

† =Pearson's chi-square test.

with generally-high healthcare utilization patterns, functional somatic syndromes (such as irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, etc.), and primary psychiatric populations themselves. As such, this study sought to examine this association; testing the hypothesis that polyallergy will be reported with statistically-significant greater frequency in those with various psychiatric and functional somatic illnesses when compared to those lacking such diagnoses. In addition, this study examined demographic, healthcare utilization, and medication patterns among those with vs without polyallergy.

METHODS

An IRB-approved retrospective electronic medical record review of all adult patients between the ages of 18 and 70 who had any clinical encounter at any

Cleveland Clinic facility between January 1, 2009 and December 31, 2014 was completed. The search mechanism used relied on the extraction of discrete data variables through use of certain proprietary data-extraction methods (E-research, Cleveland Clinic).

Demographic variables of interest included gender, age, and marital status. The number of inpatient admissions and emergency room visits served as measures of healthcare utilization. Frequency of various psychiatric and functional somatic syndrome diagnoses and frequency of certain prescribed psychotropic medication classes such as antidepressants (including tricyclic antidepressants, TCAs), anticonvulsants, mood stabilizers, stimulants, antipsychotics, and anxiolytics were collected. Patients were classified into 4 allergy groups: no allergies (0), normal allergies (1–4 allergies), polyallergy (5–9 allergies), and ultrapolyallergy (greater than 9 allergies).

TABLE 2. Healthcare Utilization and Diagnostics Summary by Allergy Category

	Full sample	No allergies (<i>n</i> = 1,423,631)	“Normal” allergies (1–4 allergies) (<i>n</i> = 549,927)	“Polyallergy” (5–9 allergies) (<i>n</i> = 29,453)	“Ultrapolyallergy” (>9 allergies) (<i>n</i> = 4423)
	<i>n</i> (%)	<i>n</i> (%) OR (95% CI)* <i>p</i>	<i>n</i> (%) OR (95% CI) <i>p</i>	<i>n</i> (%) OR (95% CI) <i>p</i>	<i>n</i> (%) OR (95% CI) <i>p</i>
Ever diagnosed with:					
Any anxiety disorder	196,256	101,818 (7.2) Ref	85,115 (15.5) 2.27 (2.25–2.29) <0.001	7922 (26.9) 4.3 (4.17–4.4) <0.001	1401 (31.7) 5.26 (4.93–5.6) <0.001
Any mood disorder	221,054	114,224 (8.0) Ref	96,422 (17.5) 2.28 (2.26–2.3) <0.001	8898 (30.2) 4.22 (4.12–4.34) <0.001	1510 (34.1) 4.86 (4.56–5.17) <0.001
Any personality disorder	6950	3236 (0.2) Ref	3089 (0.6) 2.57 (2.44–2.7) <0.001	510 (1.7) 8.41 (7.64–9.25) <0.001	115 (2.6) 13.01 (10.76–15.73) <0.001
Any psychotic disorder	14,016	7253 (0.5) Ref	6017 (1.1) 2.28 (2.2–2.36) <0.001	636 (2.2) 4.97 (4.48–5.4) <0.001	110 (2.5) 5.93 (4.89–7.18) <0.001
Any functional somatic syndrome/symptom diagnosis	82,766	34,478 (2.4) Ref	41,166 (7.5) 3.04 (3.0–3.09) <0.001	5871 (19.9) 8.55 (8.29–8.82) <0.001	1251 (28.3) 13.0 (12.16–13.9) <0.001

Values presented as *n* (column %).

Diagnoses included in analysis: **Anxiety disorder:** “anxiety,” “general anxiety disorder,” “panic disorder,” “obsessive compulsive disorder,” “post-traumatic stress disorder.” **Mood disorder:** “depression,” “major depressive disorder,” “bipolar disorder,” “adjustment disorder,” “dysthymic disorder,” “mood disorder (not otherwise specified).” **Personality disorder:** “personality disorder.” **Psychotic disorder:** “psychotic disorder,” “schizoaffective disorder,” “schizophrenia,” “delusional disorder.” **Functional Somatic Syndrome/Symptom Diagnosis:** “irritable bowel syndrome,” “chronic fatigue,” “chronic pain,” “conversion disorder,” “factitious disorder,” “somatization disorder,” “hypochondriasis,” “somatoform disorder.”

* Odds ratios and *p* values from multiple logistic regression analyses, adjusted for age and sex.

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Descriptive statistics stratified by allergy group were calculated, and demographic comparisons among the groups were made using one-way analysis of variance or Pearson's chi-square test. Zero-inflated negative binomial regression analysis was used to compare incidence rates of emergency room visits and inpatient admissions over the study period among allergy groups.

This analysis simultaneously models odds of an event occurring at all (i.e., odds of any ER [emergency room] visit or inpatient admission) and incidence of events when they occur (i.e., exact number of ER visits or inpatient admissions). Results are expressed as odds ratios (OR) and incidence rate ratios (IRR) with 95% confidence intervals (CI).

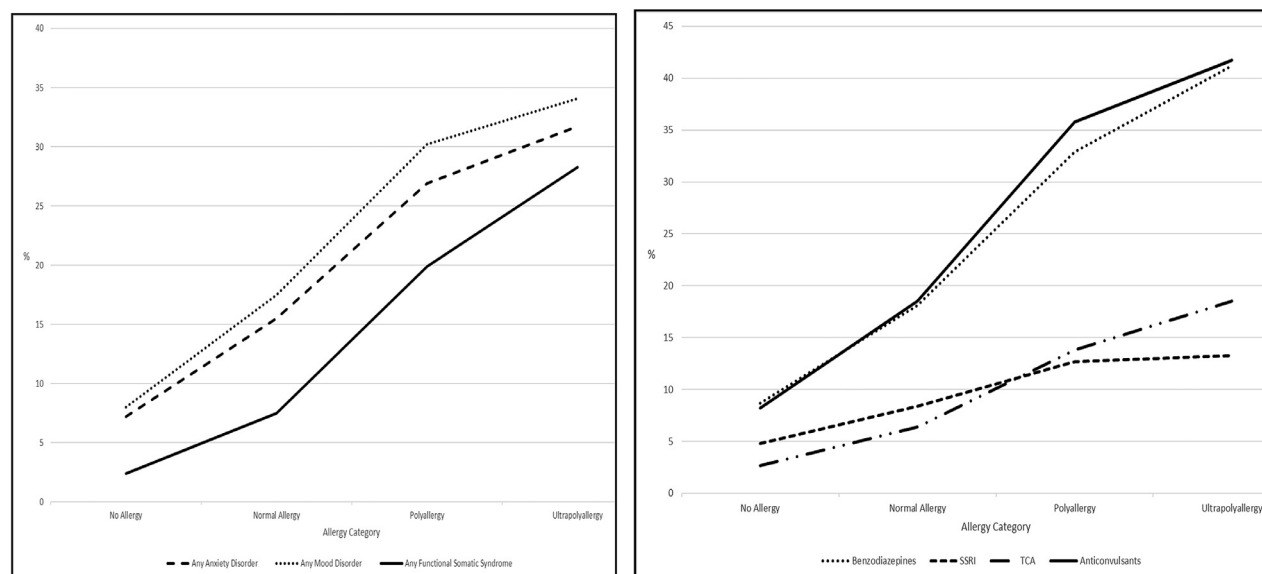
TABLE 3. Medication Summary by Allergy Category

	Full sample	No allergies	"Normal" allergies (1–4 allergies)	"Polyallergy" (5–9 allergies)	"Ultrapolyallergy" (>9 allergies)
		(n = 1,423,631)	(n = 549,927)	(n = 29,453)	(n = 4423)
	n(%)	n(%) OR (95% CI)*	n(%) OR (95% CI)*	n(%) OR (95% CI)*	n(%) OR (95% CI)*
Ever prescribed:			p	p	p
Stimulants	47,818	29,159(2.0) Ref	17,059(3.1) 1.77 (1.73–1.8) <0.001	1361(4.6) 3.27 (3.09–3.46) < .001	239(5.4) 4.32 (3.78–4.93) < .001
Benzodiazepines	234,955	124,025 (8.7) Ref	99,405 (18.1) 2.21 (2.19–2.23) <0.001	9701 (32.9) 4.67 (4.55–4.79) <0.001	1824 (41.2) 6.46 (6.08–6.86) <0.001
Mood stabilizers	29,179	15,565(1.1) Ref	11,962(2.2) 2.01 (1.96–2.06) <0.001	1398(4.7) 4.49 (4.24–4.75) <0.001	254(5.7) 5.49 (4.83–6.24) <0.001
Serotonin selective reuptake inhibitors	118,604	68,290(4.8) Ref	45,977(8.4) 1.6 (1.58–1.62) <0.001	3750(12.7) 2.17 (2.1–2.25) <0.001	587(13.3) 2.13 (1.95–2.32) <0.001
Tricyclic antidepressants	78,072	38,137 (2.7) Ref	35,060 (6.4) 2.22 (2.19–2.25) <0.001	4055 (13.8) 4.53 (4.37–4.69) <0.001	820 (18.5) 6.07 (5.62–6.56) <0.001
Atypical antipsychotics	65,593	33,183 (2.3) Ref	28,588 (5.2) 2.29 (2.25–2.33) <0.001	3233 (11.0) 5.22 (4.92–5.31) <0.001	589 (13.3) 6.37 (5.83–6.95) <0.001
Typical Antipsychotics	130,281	67,364 (4.7) Ref	56,412 (10.3) 2.16 (2.13–2.19) <0.001	5560 (18.9) 4.04 (3.92–4.17) <0.001	945 (21.4) 4.54 (4.22–4.88) <0.001
Anticonvulsants	230,728	116,787(8.2) Ref	101,538 (18.5) 2.35 (2.32–2.37) <0.001	10,558 (35.8) 5.24 (5.11–5.37) <0.001	1845 (41.7) 6.35 (5.97–6.75) <0.001

Values presented as n (column %).

Medications included in analysis: **Stimulants:** "amphetamine", "dextroamphetamine", "methylphenidate", "pemoline", "adderall", "cylert", "dexedrine", "ritalin." **Benzodiazepines:** "alprazolam", "ativan", "centrax", "chlordiazepoxide", "clonazepam", "diazepam", "klonopin", "librium", "lorazepam", "oxazepam", "prazepam", "serax", "valium", "xanax." **Mood Stabilizers:** "carbamazepine", "divalproex sodium", "lithium carbonate", "lithium citrate", "valproic acid", "depakene", "depakote", "eskalith", "lithobid." **Serotonin-specific reuptake inhibitors (SSRIs):** "escitalopram", "fluoxetine", "paroxetine", "sertraline", "fluvoxamine", "citalopram hydrobromide", "celexa", "lexapro", "prozac." **Tricyclic antidepressants (TCAs):** "desipramine", "imipramine", "amitriptyline", "amoxapine", "doxepin", "maprotiline", "nortriptyline", "protriptyline", "trimipramine", "adapin", "desyrel", "elavil", "endep", "ludomil", "norpramin", "pamelor", "sinequan", "surmontil", "tofranil", "vivactil." **Atypical Antipsychotics:** "aripiprazole", "clozapine", "olanzapine", "quetiapine", "risperidone", "abilify", "risperdal", "seroquel", "zyprexa." **Typical Antipsychotics:** "chlorpromazine", "fluphenazine", "haloperidol", "loxapine", "compazine", "mesoridazine", "molindone", "perphenazine", "prochlorperazine", "thioridazine", "thiothixene", "trifluoperazine", "haldol", "haldol decanoate", "loxitane", "mellaril", "moban", "navane", "prolixin", "prolixin decanoate", "serenitil", "stelazine", "thorazine", "trilafon." **Anticonvulsants:** "banzel", "carbatrol", "celontin", "dilantin", "ethosuximide", "felbamate", "felbatol", "gabapentin", "neurontin", "gabitril", "rufinamide", "tegretol", "methsuximide", "zarontin", "tiagabine hcl", "lamictal", "lamictal odt", "lamictal xr", "lamotrigine", "levetiracetam", "keppra", "keppra xr", "lyrica", "pregabalin", "oxcarbazepine", "trileptal", "peganone", "ethotoin", "phenytoin sodium", "primidone", "mysoline", "sabriil", "vigabatrin", "topamax", "topiramate", "valproic acid", "stavzor", "vimpat", "lacosamide", "zonisamide", "zonegran"

* Odds ratios and p values from multiple logistic regression analyses, adjusted for age and sex.

TABLE 4. Summary of Select Diagnostic and Pharmacological Frequencies Across Allergy Groups

Multivariable logistic regression analysis was used to determine whether odds of having an anxiety, mood, personality, psychotic, or functional somatic syndrome diagnosis differed among allergy groups, while controlling for age and sex. The same procedure was used to determine relative odds among allergy groups of ever having been prescribed stimulants, benzodiazepines, mood stabilizers, serotonin selective reuptake inhibitors, tricyclic antidepressants, atypical or typical antipsychotics, or anticonvulsants. Results are expressed as odds ratios with 95% CI.

Because of the large size of the dataset, very small *p* values were expected when testing associations between variables. Considering this, interpretation of results should focus on quantification of the magnitude of relationships among variables (OR and IRR). A sensitivity analysis was carried out to evaluate the cut points chosen to designate allergy groups. Four alternatives to the cutoffs as defined for the current study were considered: shifting all cut points 2 units lower, 1 unit lower, 1 unit higher, and 2 units higher. The area under the receiver operating characteristic curve was used to evaluate cut points. An increase in the area under the receiver operating characteristic curve of .01 or greater when compared to the study cut points would be considered

meaningfully improved and a change in cut points considered. Analyses were conducted on complete cases using SAS Studio v. 3.5, with alpha set to 0.05.

RESULTS

The sample included 2,007,434 patients and was 55% female with a mean age of 45.1 (SD 14.7). As displayed in Table 1, mean age increased across allergy cohorts, from 44.3 years of age in the “no allergy” group to 52.4 years of age in the “ultrapolyallergy” group. Similarly, female gender was more common with increasing numbers of allergies, with 51% of the “no allergy” group being female whereas 89.6% of the “ultrapolyallergy” group was female ($p < 0.001$). Percentages of those either married or partnered were comparable across allergy cohorts, but roughly double the percentage of patients in the ultrapolyallergy group were single, divorced, widowed, or legally separated, when compared to the no allergy group ($p < 0.001$).

Healthcare Utilization

A total of 25% of the sample had at least one ER visit over the study period, and 14% of the sample had at

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least one inpatient admission. After adjusting for the effects of age and sex and comparing to the no allergy group, those with normal allergies had 85% higher odds of having at least one ER visit (OR 1.85, 95% CI 1.84–1.86, $p < .001$), and those with polyallergy and ultrapolyallergy each had roughly two-and-a-half times the odds of having at least one ER visit (OR 2.54, 95% CI 2.48–2.6, $p < 0.001$; and OR 2.63, 95% CI 2.47–2.8, $p < .001$, respectively). Among those with at least one ER visit, after controlling for age and sex, and comparing to the no allergy group, the normal allergy group had a 3% lower rate of ER visits over the study period (IRR 0.97, 95% CI 0.96–0.99, $p < 0.001$), the polyallergy group had two-and-a-half times higher rate (IRR 2.53, 95% CI 2.49–2.57, $p < 0.001$), and the ultrapolyallergy group had nearly 4 times the rate of ER visits (IRR 3.74, 95% CI 3.64–3.84, $p < .001$).

After adjusting for the effects of age and sex and comparing to the no allergy group, those with normal allergies had more than twice the odds of having at least one inpatient admission (OR 2.31, 95% CI 2.29–2.33, $p < 0.001$), those with polyallergy had 4 times the odds (OR 4.05, 95% CI 3.95–4.15, $p < 0.001$), and those with ultrapolyallergy had 5 times the odds of having at least 1 inpatient admission (OR 4.91, 95% CI 4.62–5.22, $p < 0.001$). Among those with at least 1 inpatient admission and after adjusting for age and sex, when compared to the no allergy group, the normal allergy group had a 30% lower rate of inpatient admissions (IRR 0.71, 95% CI 0.7–0.73, $p < 0.001$), the polyallergy group had twice the rate (IRR 1.91, 95% CI 1.86–1.95, $p < 0.001$) and the ultrapolyallergy group had two-and-a-half times the rate of inpatient admissions (IRR 2.56, 95% CI 2.47–2.65, $p < 0.001$).

Diagnoses

When adjusting for the effects of age and sex, increasing odds of psychiatric and functional somatic syndrome diagnoses were observed with increasing allergies, with the strongest effects observed when considering personality disorders and functional somatic syndrome diagnoses as outcomes (Table 2). In summary, when compared to the no allergy group, the normal allergy group had over double the odds of having received anxiety, mood, personality, or psychotic diagnoses, and 3 times the odds of a functional somatic syndrome diagnosis (all $p < 0.001$). The polyallergy group

had 4–5 times the odds of having received an anxiety, mood, or psychotic diagnosis, and eight-and-a-half times the odds of a personality or functional somatic syndrome diagnosis, when compared to the no allergy group (all $p < 0.001$). Finally, the ultrapolyallergy group had 5–6 times the odds of having received an anxiety, mood, or psychotic diagnosis, and 13 times the odds of a personality or functional somatic syndrome diagnosis, again when compared to the no allergy group (all $p < 0.001$).

Medications

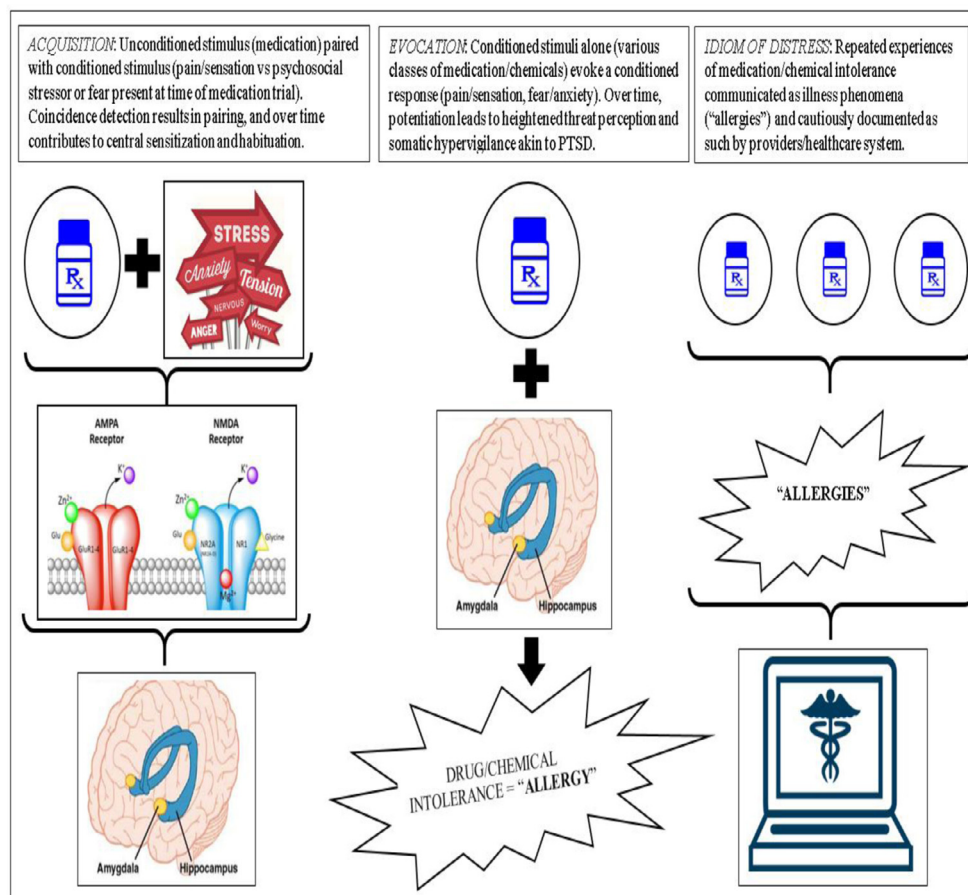
When adjusting for the effects of age and sex, odds of use of psychotropic agents increased with increasing allergies (Table 3). The strongest effects were observed when considering benzodiazepines, TCAs, atypical antipsychotics, and anticonvulsants as outcomes. The polyallergy group had twice the odds of having been prescribed serotonin-specific reuptake inhibitors (SSRIs); 3 times the odds of stimulants; 4–5 times the odds of benzodiazepines, mood stabilizers, TCAs, and typical antipsychotics; and over 5 times the odds of atypical antipsychotics and anticonvulsants, when compared to the normal allergy group (all $p < 0.001$). The ultrapolyallergy group had twice the odds of having been prescribed SSRIs; four to four-and-a-half times the odds of stimulants and typical antipsychotics; five-and-a-half times the odds of mood stabilizers; and greater than 6-fold odds of benzodiazepines, TCAs, atypical antipsychotics, and anticonvulsants, when compared to the normal allergy group (all $p < 0.001$).

Sensitivity Analysis

No alternative set of cut points examined yielded an area under the receiver operating characteristic curve 0.01 higher than the area under the receiver operating characteristic curves generated using the cut points predefined for this study. This held for all outcomes examined.

DISCUSSION

This study reveals a clear, statistically-significant association between increasing patient-reported, chart-documented adverse drug reactions (or “polyallergy”) and various demographic, diagnostic, pharmacological, and healthcare utilization trends (Table 4). These findings

FIGURE 1. Biological, Psychological, and Social Mechanisms Involved in the Development of Polyallergy/Multiple Chemical Sensitivity

are important as they suggest certain clinically-relevant expectations emerging from greater and greater self-reported or documented allergies. Increasing polyallergy, alongside other clinical data, may facilitate clinical interventions, such as the consideration of mental or behavioral health approaches.

Some of these findings have been demonstrated in comparable studies. In a retrospective analysis by Macy *et al.*⁶ of over 450,000 patients with at least one reported allergy, MDIS (defined broadly as anyone with 3 or more unrelated drug class allergies) was present more often in older, female, high utilizers of healthcare with increased rates of anxiety. Similarly, Omer *et al.*⁹ reviewed a sample of 25,000 patients with at least 1 reported allergy, finding that MDIS was more common in females with high comorbidity and healthcare utilization. The study here thus replicates these associations, strengthening their merit.

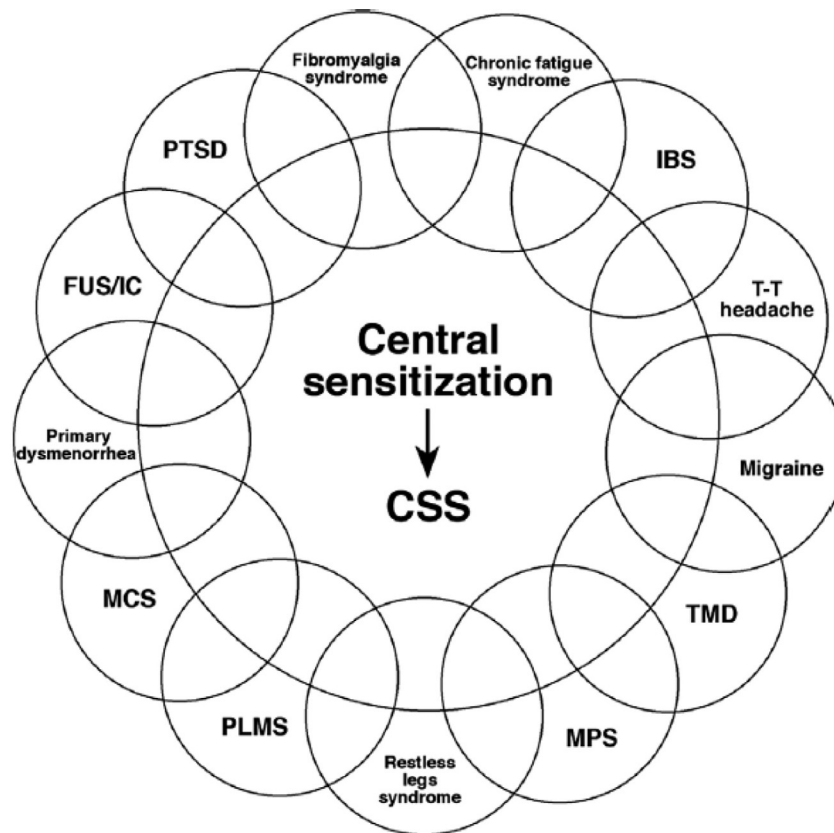
Before exploring the reasons for these associations, it is important to note this study's strengths and limitations. The study is powered by a very large clinical sample (over 2 million patients), allowing for detection of associations and statistical significance despite the presence of many confounders. This study is also inclusive of a naturalistic group, namely, all patients with a documented clinical encounter within a given large medical system. The study time period spans 6 years. Additionally, this study examined discrete data across multiple realms (demographic, medical, psychiatric, pharmacological, and healthcare utilization), offering a multidimensional understanding of those with polyallergy.

There are several limitations to this study. A retrospective design introduces limitations in the data that is examined. The crude capture of documented allergies raises various issues as well, ranging from the veracity of the allergies themselves to the highly patient- and

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FIGURE 2. Central Sensitization as an Implicated Mechanism in Multiple Allergies, Mental Health Disorders, and Functional Somatic Syndrome Disorders

FUS = female urethral syndrome/chronic pelvic pain; IBS = irritable bowel syndrome; IC = interstitial cystitis; MCS = multiple chemical sensitivity; MPS = myofascial pain syndrome; PLMS = periodic limb movements in sleep; PTSD = posttraumatic stress disorder; RSTPS = regional soft-tissue pain syndrome; TMD = temporomandibular disorders; T-T headache = tension-type headache. Reprinted from "Yunus MB. Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes. *Seminars in Arthritis Rheumatology*. 2007; 36(6):339–356," with permission from Elsevier; license number 4332711403998 (April 19, 2018).



operator-dependent nature of documentation of said allergies. Despite being based on previous studies^{2,3} as explained in the methodology section, the chosen allergy count cohort definitions were arguably arbitrary, even after completion of the sensitivity analysis utilized here. Patients studied were also limited to 1 clinical site, questioning the generalizability of the results. Healthcare utilization is also a complex metric, and information regarding any utilization outside of this clinical site was not available. Furthermore, the impact of clinician behavior on allergy documentation is complex and a confounder. Finally, medications listed under certain categories may have been used for reasons outside of that category. For instance, benzodiazepines

are used for seizures, detoxification, agitation, isolated phobias (e.g., claustrophobia in preparation for radiological studies), and many other reasons beyond general anxiety treatment. Despite these limitations, this study replicates previous findings^{6,9} and its large sample size accounts for the detection of significant and generalized trends surpassing the effects of confounders.

Potential Mechanisms

Although no direct causality can be assigned to any individual demographic or clinical variables examined, this study's associations assist in generating certain hypotheses. With advancing age, patients may simply

accumulate larger numbers of clinical encounters over time, resulting in more drug exposures and thus greater instances for “allergy” documentation. In terms of gender, it has been previously reported that females experience greater numbers of allergic responses to medications than men,^{6,9} though the mechanisms for this difference are varied and complex. First, it is known that women utilize greater numbers of medications overall than do men, as evidenced by large-scale epidemiological studies,¹¹ thereby providing greater opportunities for both physiological vs perceived allergic reactions. Second, female preponderance of certain immunologically-mediated allergic conditions, namely respiratory ones such as allergic rhinitis and asthma, have been demonstrated to be due to complex sex differences in interleukin and hormonal function.¹² This physiologically-based difference, however, has not been noted in drug-related allergies or intolerances when examined epidemiologically,¹³ turning attention instead to psychological and/or sociocultural explanations such as the relationship between gender and distress communication and healthcare utilization. As noted, those with increased numbers of allergies found themselves more engaged with acute health delivery services. It is unclear if increasing perceived allergic responses are occurring as a result of increased healthcare encounters (as previously suggested might occur over time with advancing age), or if some of the encounters (particularly acute care ones) are themselves sought in order to manage allergic responses. More medical encounters equates to increased opportunities for drug reactions and allergies to be documented, whether accurately or not, as most acute services will include allergy reviews in routine intakes and evaluations. Of note, healthcare utilization is also generally higher in females than among males¹⁴; reasons for this difference are socioculturally complex and beyond the scope of this study, though the known greater tendency among females to both experience distress and to seek reassurance from medical contexts is likely at play.¹⁵ Interpersonally, this study's finding of significantly higher numbers of single, divorced, widowed, or legally-separated patients among “ultrapolyallergy” groups is suggestive of a possible mediator within poor relational functioning, lack of social support, or both. Such interpersonal states impact healthcare utilization, with numerous studies demonstrating certain insecure attachment relational styles (such as anxious, fearful, avoidant, etc.) resulting in aberrant healthcare use patterns.¹⁶

Indeed, in the absence of more adaptive social supports, such patients often maladaptively seek interpersonal needs in clinical and medical rather than family or other social settings.¹⁷

This study generates questions regarding the role of mental health and functional somatic syndrome disorders. Our findings parallel those of numerous other studies in terms of high rates of anxiety and/or depression among patients with higher numbers of reported allergies.^{6–8,18–20} These conditions are associated with highly-reinforced classical and operant conditioning mechanisms,^{21,22} including specific placebo/nocebo reactions,²³ heightened threat perception,²⁴ and possibly frank posttraumatic stress disorder (PTSD).²⁵

Mechanisms such as stimulus and context generalization may inform pathophysiology, as loosely-associated or accompanying stimuli can confound drug intolerances (e.g., co-occurring disease sensations/other physiological phenomena or environmental/psychosocial stressors, respectively, may influence stimuli that are then generalized to the taking of medication or the sensations associated with medication). Stages of conditioning may occur until all or many different medications or sensations result in similar, highly-reinforced aversive responses²⁶ (Figure 1). At the molecular level, such long-term potentiation and conditioning occurs via the relationship between magnesium blockade of N-Methyl-D-Aspartate receptors and nearby α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, a phenomenon termed coincidence detection.²⁷ This mechanism has also been implicated in traumatic learning, such as in PTSD, a condition also defined by high somatic and interoceptive vigilance.²⁵ In patients with numerous unexplained allergies, a medication may trigger somatic hypersensitivity which is centrally misconstrued as threatening by involuntary activation of highly-conditioned and subcortical fear-processing systems (such as the amygdala/hippocampus complex) with little-to-no cortical input to balance the “threat.”²⁸ A patient may thus interpret normal effects of an externally-introduced medication as uncomfortable even if benign and expected; in the absence of more adaptive coping strategies (a common predicament in PTSD but also depressive and other anxiety disorders), this may result in an exaggerated subjective sense of intolerance, loss of control, or even despair. A somatic parallel to PTSD may occur: the objectively benign yet subjectively catastrophic sensation is preconsciously

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reminiscent of past trauma (somatic reliving), thus triggering side effect anticipation (hypervigilance) and medication refusal (avoidance). Each visceral incident likely reinforces the patient's symptom hypervigilance and medication avoidance, resulting in accumulated "adverse" experiences.²⁹ This model would require further psychophysiological information corroborating stress-reaction symptoms. Unfortunately, our study did not include information on the rates of trauma in patients to further corroborate the PTSD model, nor could it have possibly examined patterns of classical/operant conditioning. Nonetheless, this conceptualization of placebo/nocebo expectations, phobic/conditioned responses, and posttraumatic pathophysiology may prove clinically useful despite warranting further investigational corroboration.

Similarly, functional somatic syndrome disorders such as fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, chronic pain, postural orthostatic tachycardia syndrome, and somatoform disorders generally feature high somatic or interoceptive vigilance, with high degrees of comorbidity with trauma and PTSD. Of note, studies have directly linked multiple allergies with specific functional somatic syndrome disorders (fibromyalgia, chronic fatigue syndrome).⁴ Furthermore, the notion of central sensitization, or abnormal and intense enhancement of pain and other somatic stimuli in the central nervous system,³⁰ has been implicated in such disorders as well as in depression, anxiety/PTSD, and MCS/MDIS. Similarly with long term learning and potentiation, central sensitization itself is also noted to occur molecularly via N-Methyl-D-Aspartate receptor activation.³¹ At least 2 studies have specifically demonstrated robust experimental evidence of central sensitization in MCS.^{32,33} Greater awareness of central sensitization has led to a neurobiological and parsimonious reconceptualization of conditions and diagnoses traditionally thought of as separate, and instead are reconsidered as a broader "central sensitization syndrome,"³⁴ as depicted in Figure 2. Interestingly, somatization disorder was not identified at all in our study's large cohort, a reflection of the DSM-IV diagnostic construct's impracticality given its very strict 4-organ involvement minimum system criteria and high stigma; this impracticality has been previously demonstrated in other large population studies³⁵ and was a driving force in changes towards "somatic symptom disorder" reclassification in DSM-5.

Pharmacologically, benzodiazepines and anticonvulsants were each prescribed in over 40% of all ultrapolyallergy patients. These agents conjointly suggest a pharmacological correlate to addressing central sensitization and/or anxiety indirectly as both benzodiazepines and anticonvulsants bluntly suppress central nervous system activity, thereby reducing somatic/interoceptive hyperarousal acutely, albeit with significant side effects, and long-term problems. Interestingly, SSRIs are the FDA-indicated and effective treatment for severe anxiety disorders such as panic disorder and PTSD, yet their prescription rates were significantly lower than that of most other agents in this study. The reasons for this discrepancy are unclear, though likely involved is stigma associated with chronic/continuous SSRI use (as opposed to preferred medicalization of anxiety under other nonpsychiatric diagnostic labels and/or only periodic/reactive benzodiazepine and/or anticonvulsant use). Further studies are required to confirm any additional correlations among medication use and allergy counts.

Socially, this study suggests that polyallergy ultimately may represent a medicalized, patient-derived behavior serving as a communication proxy for internal distress or anxiety. Such somatization of anxiety has been examined across cultures and is corroborated with the idiom of distress theory.³⁶ However, for allergies to accumulate in a given patient's record, they must also be documented by clinicians (Figure 1). Reasons for over-documenting allergies without full corroboration include concerns for legal repercussions (i.e., defensive medicine)^{37,38} and incorrect methods by those involved in documentation itself (including a variety of involved clinicians ranging from medical assistants to nurses and medical students/residents to full staff).^{39,40}

Ultimately, further studies are needed to better understand polyallergy as a phenomenon. Many immune-mediated mechanisms, though collectively rather rare, could ideally be assessed in patients with polyallergy, including anaphylaxis, drug reactions with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, or severe forms of hypersensitivity such as Stevens–Johnson syndrome/toxic epidermal necrolysis.⁴¹ Furthermore, there may be pharmacodynamics or pharmacokinetic mechanisms involved that we are unaware of. This study's findings and discussion ultimately offer a potential, multidimensional mechanistic overview to polyallergy (Figure 1) which warrants further examination and study.

Potential Management

This study also suggests certain management considerations for patients with polyallergy. If mental health comorbidities, somatic/interoceptive hypervigilance, and/or other features are identified, it may be prudent to educate patients about PTSD, central sensitization and other pathophysiological mechanisms involved in medication intolerance, distinguishing this phenomenon from immune-mediated hypersensitivities. This may lead to a transparent re-evaluation of allergy lists with the patient, safe retesting of medications in supervised settings or clinics, and eventual removal of incorrectly-documented allergies. Medication retesting has been previously performed: in a cohort of 480 patients with MDIS and known negative allergy test results, retesting revealed negative allergic responses in 87% of retests, while those few with allergic responses were mild in severity and easily managed with oral antihistamines or corticosteroids.⁴² Once determined that an allergy is unwarranted, it is clinically suggested that it be removed in order to offer greater pharmacological opportunities for future healthcare providers.⁴³ Certain approaches such as mindfulness-based stress reduction (MBSR) may address shared pathologies such as central sensitization, anxiety, and somatic hyperarousal. MBSR has been shown to be effective in managing

stress,⁴⁴ anxiety,^{45,46} fibromyalgia,⁴⁷ and chronic pain.⁴⁸ As applied to polyallergy, 1 study demonstrated statistically-significant improvements among women with comorbid MCS, chronic fatigue syndrome, and fibromyalgia exposed to MBSR as compared to a control group receiving usual care.⁴⁹

CONCLUSIONS

This study demonstrates that polyallergy/MCS is multifactorial yet may very well signal accompanying psychopathology and/or abnormal illness behavior. Efforts should be made to correlate polyallergy with other risk factors, such as comorbid psychiatric or functional somatic syndrome disorders. Examination of the role of central sensitization and other drivers is warranted. Educating patients about polyallergy and challenging inappropriately-perceived allergies is also justified. Further investigations are needed to enhance the associations identified by this study.

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