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Using a pilot-centric, qualitative drug risk assessment model to identify opportunities for implementing pharmacogenetics

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Abstract

Background: Risk assessment models are at the core of flight medicine, weighing both the impact of the flight environment on an aviator and the potential impact of medical events in aviators on flight operations. Pharmacogenetics is the application of a patient's genetic information to reduce medication risk. Here, we use three medical conditions commonly encountered by the U.S. Air Force's flight medicine community (asthma, diabetes, and hypertension) to demonstrate a framework for implementing occupationally relevant pharmacogenetics. We identified medications approved by the U.S. Food & Drug Administration for each condition, obtained adverse effects and frequencies, scored each adverse effect's impact on work duties from 0 to 4 in increasing severity, and used control theory to stratify the medications by occupational risk. For those medications within 10% of the control limits, pharmacogenetic information was collected from PharmGKb.

Results: We observed a correlation of 0.557 between our risk scores and previous reports for 20 medications, demonstrating robustness of our scoring. Using average risks for those 20 medications, we set control theory acceptable and tolerable thresholds at 601,109.5 and 2,097,721, respectively. The majority of medications for the three conditions were below the thresholds (66 and 26, respectively). Three medications have pharmacogenetic guidance provided by regulatory bodies.

Conclusions: By focusing first on risk to performing occupational tasks and then on genetic implementation, our work presents a framework by which pharmacogenetics can be selectively applied by considering specific occupational and environmental risks, thereby saving costs and reducing possible psychological burdens on patients.

Background

Risk assessment models are at the core of occupational medicine, and specifically aviation medicine. Weighing both the impact of the flight environment on an aviator and the potential impact of medical events in aviators, such risk assessments include all aspects of flight operations and are intended to reduce harm to the patient, airframe, and any passengers or cargo transported in the aircraft. Aviation exposes aircrew to repeated environmental hazards to which the human body is largely unaccustomed and medical conditions that are only mildly distracting in normobaric and normoxic environments could have disastrous consequences in the flight environment. Practitioners of flight medicine, therefore, face a unique challenge: evaluating and reducing medical risks from conditions affecting aircrew while also considering the effects of any treatment on flight readiness.

To that end, several approaches to risk assessment have been developed [1–3]. These early risk assessment approaches have evolved to the recent presentation of a multi-dimensional matrix for medical conditions, which

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considers the frequency of a medical event's occurrence, the potential consequence upon flight operations, and the role of the aviator-patient [4]. Similarly, a systematic aeromedical risk assessment for medications was developed by the U.S. Navy [5] and modified by the U.S. Air Force [6]. Systematic risk assessments like those presented by Prudhomme [5], Huntsberger [6], and Gray [4] provide crucial insight into reducing aeromedical risk toward the 1% Rule (1 incapacitating event in 100 person-years) [4]. However, none consider the individual patient's unique genetic predispositions to conditions or medication responses.

Asthma, diabetes, and hypertension each pose health and safety concerns in the aviation environment. An asthma exacerbation or hypoglycemic episode during flight can be catastrophic, especially if an aviator is alone at the controls. Even the subtle nature of hypertension causes concern. Untreated, hypertension can lead to myocardial infarction or cerebrovascular incidents. The aviation environment also involves stressors that can aggravate these conditions. For example, the cool dry air on an aircraft can trigger an asthma exacerbation in undertreated asthmatic aviators [7]. Even mild blood sugar abnormalities can negatively impact performance of complex cognitive tasks such as flying an aircraft while communicating with Air Traffic Control [8].

Additionally, a comparison between efficacy and safety (e.g., adverse effect profile) is an important consideration. For example, certain classes of diabetes medications are more likely to precipitate hypoglycemic episodes [9]. Other common medication adverse effects like somnolence or diarrhea are not appropriate in the aviation environment as they can lead to reduced alertness and/or distraction.

The aim of our study was to develop a potential framework for implementing pharmacogenetics in an occupational medicine specialty without requiring massive large-scale genetic screening. Here, we present a two-fold approach to estimating and minimizing aeromedical risks of pharmaceutical treatments. We first present an extension of a pilot-centric drug risk assessment model for considering medications used when treating asthma, hypertension, and diabetes. We then employ that risk assessment model to identify which medications the flight surgeon should consider pharmacogenetics when developing risk minimization strategies for individual patients.

Methods

We used three medical conditions commonly encountered by the U.S. Air Force's Aeromedical Consultation Service to demonstrate a possible application of pharmacogenetics in the practice of aerospace medicine. First, we evaluate the risks posed to flight operation by certain medications. Then, we identify how precision medicine could guide utilization of these medications, in an effort to minimize risk.

Medication selection

We selected medications to evaluate using two approaches. In one approach, we searched the PharmGKb database [10] for the condition of interest and identified medications with reported pharmacogenetic findings. In the second approach, we searched the website drugs.com by condition of interest for US Food and Drug Administration (FDA)-approved medications [11]. Only medications approved for use as of January 2021 in the United States were included in the review and off-label uses were not considered.

Adverse effect risk assessment

We performed an adverse effect risk assessment calculation using a standardized approach first reported by Prudhomme in 2015 for the US Navy [5] and Huntsberger in 2017 for the US Air Force [6]. Adverse effects and their frequencies were identified for each medication using Drugs.com (updated as of September 14, 2020). In cases where the adverse effect frequencies were reported differently, we used the following procedure to adjudicate frequencies [6]: 1) ranges within a study were assigned to the highest level of incidence; 2) ranges between studies were assigned to an arithmetic mean; 3) when data were reported as "less than" in one source but another source provided a range or percentage, the data from the latter source were used; 4) when data were reported in all sources as "less than 1%," the frequency was scored zero as no mean could be calculated (in the case of "less than a small percentage greater than 1%," frequency was scored 1%); and 5) studies reporting adverse effect "equal to or less than placebo" resulted in zero scores.

Using the Prudhomme method of an aircrew-centric model, [5] we assessed the risk of each adverse effect against flight operations. Each adverse effect was given an impact severity multiplier from 0 (no aeromedical concern) to 4 (totally incapacitating) by three experienced flight surgeons independently and the three scores were averaged to provide the final severity multiplier. The adverse effects were provided in a single list without association to any medication to reduce unconscious treatment bias. Similar to Prudhomme and Huntsberger, we calculated an overall weighted risk score for each medication. Briefly, each adverse effect was scored independently as a multiplication of the severity multiplier and the reported effect frequency. The individual effect scores were summed to yield an overall medication risk score.

We rescored the drugs from the Prudhomme study to establish the model's mean adverse effect risk score, upper allowable ("acceptable" score) limit (UAL = mean + 1.5 standard deviation (SD)), and upper control ("tolerable" score) limit or maximum tolerable adverse effect risk (UCL = mean + 3.0 SD).

Pharmacogenetic recommendations

Using the aforementioned PharmGKb database, for each medication we gathered variant annotations, clinical annotations, and drug label annotations. Excluded from the review were associations between medications and conditions not related to diabetes, hypertension, or asthma. For example, the diabetes medication liraglutide has been associated with glucagon-like peptide 1 receptor (GLP1R) CT and TT genotypes in obese women with Polycystic Ovarian Syndrome [12], but that pharmacogenetic information was not included in our study. We compared levels of evidence in accordance with the PharmGKb recommended levels, increasing in strength from level 4 (non-human studies) to level 1A (clinical guidance issued). Although we only searched for FDA-approved medications, we report prescribing recommendations issued by any international clinical body.

Results

Adverse effect risk scoring

We had three aeromedical experts score the individual adverse effects. All three were board-certified flight surgeons and had already completed or were in the process of completing a second graduate residency in aerospace medicine. In total, we collected 1,152 individual adverse effects for scoring. Of these, 297 (25.8%) were scored the same by all three experts, while another 627 (54.4%) were scored within only a single score being different by one risk level (e.g., one expert scored "mildly distracting" while the other two scored "distracting"), and the remaining 228 (19.8%) had a larger discrepancy between judges. Collectively, 924 were scored the same by at least 2 of the 3 physicians with the disagreeing physician only providing an alternate score within 1 severity level.

We calculated the inter-rater reliability in R using Fleiss' kappa for 3 raters and Krippendorff's alpha. Overall, we observed fair reliability over the 1,152 side effect ratings with both kappa and alpha being 0.294. This observation reflects the greatest limitation to the systematic risk assessment model as adverse effect severity is a subjective measure determined by experts. The average scores for the raters were similar, although rater 1 scored adverse effects as more severe than the other two raters (rater 1 mean = 2.14 ± 1.13, rater 2 mean = 1.82 ± 1.27, rater 3 mean = 1.86 ± 1.03). Pairwise analyses of Cohen's unweighted kappa suggest that the scores are similar (rater 1 vs. 2 kappa = 0.326, rater 1 vs. 3 kappa = 0.280, rater 2 vs. 3 kappa = 0.283); however, the pairwise rater biases were 0.257, 0.288, and 0.512 for rater 1 vs. 2, 1 vs. 3 and 2 vs. 3, respectively, suggesting rater 1 was substantially different than raters 2 and 3. The pairwise percent agreement between all raters was consistent around 45% for perfect agreement (1 vs. 2 = 47.1%, 1 vs. 3 = 45.2%, and 2 vs. 3 = 44.2%) and around 88% when allowing for a deviation in severity rating of 1 score (1 vs. 2 = 90.3%, 1 vs. 3 = 88.3%, and 2 vs. 3 = 86.9%).

Overall medication risk assessment

In total, we identified 103 medications for risk assessment in the study (83 unique to the three conditions). Of the 20 medications taken from the approved list provided by Prudhomme and colleagues [5] (termed "PA"), four were also included in the other conditions (three for hypertension and one for diabetes); these medications were considered as part of the PA group for establishing control limits. The results from the blinded adverse effect scoring revealed a non-normally distributed range of scores for the PA group (Fig. 1) (mean: 235,806; standard deviation:183,126; range: 40,320–643,100; median = 212,810; excess kurtosis = 0.88; skewness = 1.28; D'Agostino-Pearson omnibus test statistic = 7.02 (P = 0.03)). The risk scores were, however, log-normally distributed (mean: 5.24; standard deviation: 0.36; range: 4.61–5.81; median = 5.33; excess kurtosis = -0.67; skewness = -0.25; D'Agostino-Pearson omnibus test statistic = 0.700 (P = 0.70)). We were therefore used the log values to establish the UAL and UCL at risk scores of 601,109.5 and 2,097,721, respectively. While the absolute scores in our study are higher than those found in the Prudhomme and Huntsberger reports (Table 1) [5, 6], our blinded scoring system proved reliable as the Pearson correlation between our scoring and the scores abstracted from Prudhomme equaled 0.557.

Using the established control limits, 75 of the 83 condition-specific medications (73%) were below the UAL (Fig. 2). Another 25 medications (24%) were between the UAL and the UCL, and the final 3 medications were above the UCL. Of the 25 mid-range medications, only a single medication (clonidine) had a score close to the UCL (within 10%). Finally, adverse effect frequencies were not available for dyphylline/guaifenesin or prednisone, so their risk scores were unable to be determined.

Pharmacogenetic evidence level analysis

Overall, we identified 34 medications with pharmacogenetic evidence across the three conditions (9 each for diabetes and hypertension, 16 for asthma). Considering the clinical annotation levels of evidence as defined by PharmGKb (Table 2), none of the medications met the

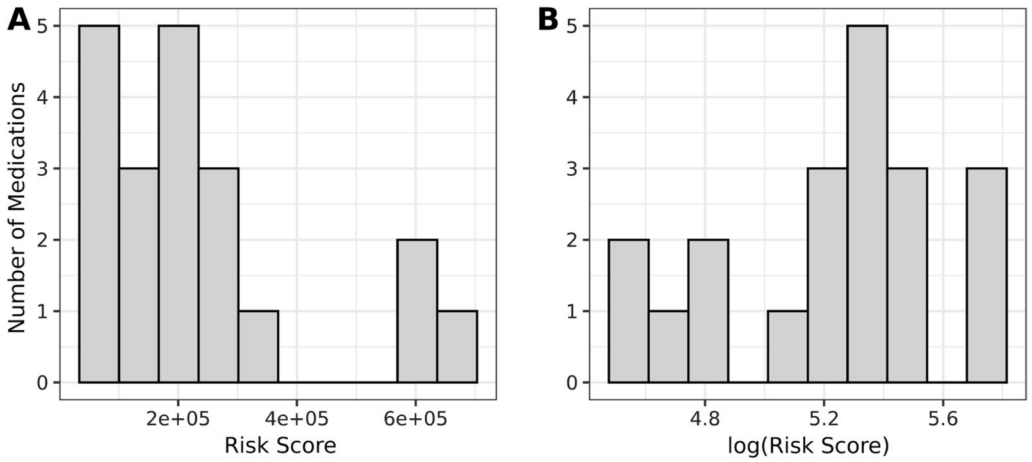

Fig. 1 Risk score distribution for PA medication list as average scores (left) and log scores (right). The raw scores are highly right skewed (skewness = 1.28), whereas the log scores are normally distributed (D'Agostino-Pearson $P = 0.70$)

level 1 condition and only four met level 2, all at level 2A (two diabetes medications, and 1 medication each for asthma and hypertension). Two more diabetes medications only had level 4 evidence, and the remaining 28 medications had level 3 evidence.

Beyond the clinical levels of evidence, the 34 medications were associated with 165 genetic variants across 86 unique genes. There were 50 variants with clinical annotations for diabetes, 70 for asthma, and 45 for hypertension. As would be expected, two drug metabolism cytochrome P450 enzymes (CYP2C8 and CYP2C9) were commonly associated with clinical evidence for asthma and diabetes, and all three conditions, respectively. Asthma and hypertension also shared the angiotensin converting enzyme (ACE) and beta-2-adrenergic receptor (ADRB2).

Discussion

A medication's risk to the patient and flight operations is a function of the severity and likelihood of each associated adverse effect. Care should be taken when considering the relative risk assessments of these drugs as the utility of the risk assessment model is limited by the manner and duration for which adverse effects have been gathered for each medication. In our analysis, only a single medication (clonidine) was found to have a adverse effect risk score within 10% of the upper control limit. Clonidine has nearly 50 years' worth of medical history from which adverse effects can be gleaned, so the number of adverse effects reported are likely reliable.

The primary limitation of this study is that there remains some subjectivity to the risk scoring as groups of specialty physicians are required to subjectively score the occupation-specific risk level. While our model is robust, the primary limitation is in the subjective determination of adverse effect impact on performing occupational tasks (e.g., flight operations). Our assessment of inter-rater reliability found that perfect agreement among three raters was approximately 25%, slightly above the expectation of 20% by chance for 5 categories. Pairwise evaluations were slightly better, approaching 50% agreements. In contrast, when a tolerance of 1 level severity level discrepancy was permitted, the global agreement percentage climbed dramatically to 77% with the pairwise agreements nearing 90%. Considering this subjectivity limitation, the intent of our findings is not to remove medications from use. Rather, by providing flight surgeons with additional patient-specific risk information from their genetic profile, our findings could enable the mitigation of unfavorable adverse effects during flight operations.

Additionally, a patient's genetic profile may result in a decreased response to a given medication. As we learn more about each medication's relationship with genetic markers, we begin to understand therapeutic window thresholds. Additionally, these thresholds may differ between aviators and the general population, another limitation of this study suggesting further work to expand the risk assessment model into other occupations. This information may suggest a need for higher dosing, which also increases the risk of adverse effects. For medications where the risk is already well below the upper allowable limit, the impact of an increased adverse effect risk will likely remain marginal. In these cases, genetic testing is not indicated. However, for the six medications with risk scores near the UCL, the physician should consider the patient's individualized response. Some patients may have a heterogeneous response requiring elevated dosage,

Table 1 Medications, risk scores and primary clinical condition. Medications contained in the Prudhomme study which are prescribed for one of the three conditions are included in the PA list

Medication	Risk Score	Medication	Risk Score	Medication	Risk Score
Asthma					
Albuterol	573,582	Formoterol	473,566.1	Prednisone	0
Beclomethasone	22,340.1	Levalbuterol	403,040	Reslizumab	112,500
Benralizumab	4100	Mepolizumab	168,900	Salmeterol	211,111
Budesonide	543,111	Metaproterenol	534,473	Theophylline	2,890,604
Ciclesonide	214,540	Methacholine	100.2	Tiotropium	739,461
Cromolyn	31	Mometasone	135,510	Triamcinolone	195,420
Dupilumab	5300	Montelukast	243,718	Umeclidinium	513,220
Dyphylline/ guaifenesin	0	Nedocromil	91,500	Zafirlukast	63,112
Flunisolide	709,287	Omalizumab	165,471	Zileuton	464,548
Fluticasone	53,400				
Diabetes					
Acarbose	322,890	Empagliflozin	4600	Pioglitazone	744,213
Albiglutide	458,142	Ertugliflozin	410,223	Pramlintide	580,200
Alogliptin	144,160	Glipizide	632,630	Repaglinide	558,800.1
Bromocriptine	658,953	Glyburide	121,261	Rosiglitazone	341,048
Canagliflozin	632,886.1	Liraglutide	1,048,504	Saxagliptin	607,510
Chlorpropamide	101,101	Metformin	1,093,373.2	Semaglutide	507,340
Dapagliflozin	116,310.1	Miglitol	288,785	Sitagliptin	113,000
Dulaglutide	455,611	Nateglinide	417,000	Tolbutamide	1020
Hypertension					
Amiloride	91,010	Diltiazem	336,361	Olmesartan	638,531
Atenolol	1,016,222	Enalapril	312,240	Perindopril	565,340.2
Benazepril	100,010	Furosemide	48,550	Ramipril	595,480.1
Bevacizumab	3,132,500	Hydralazine	224,233.1	Sorafenib	1,359,560
Bisoprolol	1,057,507	Hydrochlorothiazide	58,440	Spironolactone	215,486.2
Candesartan	204,626.1	Irbesartan	667,432	Tacrolimus	3,700,360
Captopril	544,254.2	Lisinopril	622,310	Trandolapril	712,547
Carvedilol	1,231,020.2	Losartan	643,100	Valsartan	230,701.1
Chlorothiazide	50,500	Metoprolol	1,095,114.2	Verapamil	435,440
Chlorthalidone	208,312.1	Nebivolol	781,311		
Clonidine	2,038,925	Nifedipine	737,460		
Control (Prudhomme)					
Allopurinol	103,720	Esomeprazole	181,730	Lisinopril	622,310
Amlodipine	263,990.2	Fexofenadine	40,630	Losartan	643,100
Atorvastatin	74,950	Finasteride	231,310	Meloxicam	225,270
Augmentin	143,620	Fluticasone	53,400	Ranitidine	40,320
Azilsartan	222,510	Hydrochloro-thiazide	58,440	Simvastatin	326,810
Ciprofloxacin	252,000	Ibuprofen	612,570	Valacyclovir	260,380
Doxycycline	155,950	Linagliptin	203,110		

Overall drug risk scores were calculated by summing the risk scores for each adverse effect, which were a multiplication of the effect frequency along with a severity multiplier coefficient determined by 3 board-certified flight surgeons. Details of the procedure are presented in the methods.

which may increase the likelihood of adverse effects and increase the overall risk above a tolerable level.

From a pharmacogenetics standpoint, fewer than half (34 of 82, 41.4%) of the medications for these conditions have reported information, and even fewer (3, 3.7%) have guidance from regulatory bodies. there are informative drug label annotations for tiotropium and nebivolol. The FDA drug label for tiotropium explains it was not found to inhibit several cytochrome P450 enzymes in vitro [14]. As with tiotropium, there is no recommended dosage

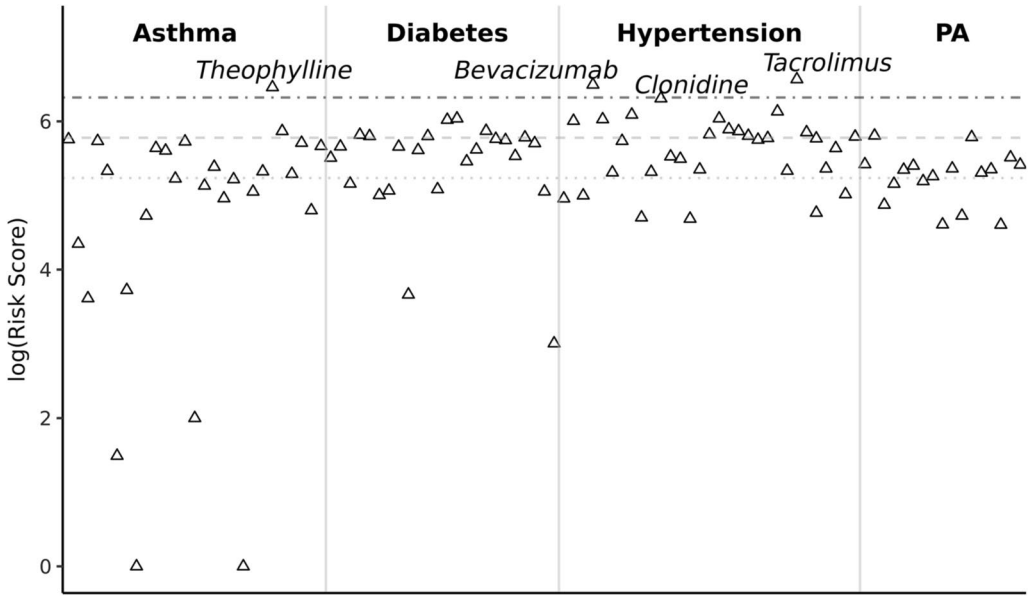

Fig. 2 Aircrew-centric adverse effect risk scores for FDA-approved medications for asthma, diabetes, and hypertension. Control lines were established using medications approved for use in flight operations as indicated by Prudhomme [5] ("PA" section). Medications above and within 10% of the upper control line (UCL) are indicated by name, all other medications and adverse effect scores are available in supplementary information. PA = medications reported as approved for use in Prudhomme's study; UAL = upper allowable limit; UCL = upper control limit. PA = medications reported as approved for use in Prudhomme's study; UAL = upper allowable limit; UCL = upper control limit

Table 2 PharmGKb clinical annotation levels. Descriptions are adapted from the PharmGKb website available at: https://www.pharmgkb.org/page/clinAnnLevels

PharmGKb Level of Evidence	Description
1A	Strongest level of evidence. At least one publication and clinical guidelines or a drug label with variant-specific prescribing guidance
1B	High level of evidence supporting the drug-variant combination, but no variant-specific prescribing recommendations. Supported by at least two independent publications
2A	Moderate level of evidence. Variants are on the PharmGKb pharmacogene list with implied causality of drug phenotypes. Supported by at least two independent publications
2B	Moderate level of evidence, possibly conflicting results. Variants are not in known pharmacogenes, but drug-variant associations have been reported in at least two independent publications
3	Low level of evidence. Variant-drug association may have been reported in only a single study, several studies may contradict an observed association, or the association is based upon preliminary evidence such as a case report or in vitro molecular studies
4	Available evidence score is negative, indicating that the evidence does not support an association between the variant and observed phenotype

adjustment to nebivolol in *CYP2D6* poor metabolizers [13]. While there is a 7 h increase in the nebivolol half-life, there is no significant change in safety or efficacy. Additionally, the European Medicines Agency (EMA) does have prescribing information for pioglitazone. Of note, the EMA recommends caution for patients with G6PD-deficiency (glucose-6-phosphate dehydrogenase) when prescribing pioglitazone [15]. As US military service members are screened for G6PD activity upon accession, this EMA recommendation provides a current example of how pharmacogenetics can be used to improve aeromedical care delivery.

Critically for our intent to use an occupationally directed risk assessment to guide pharmacogenetic testing recommendations, we found a single medication near the UCL where patient-specific information may help guide care management. As an example implementation of our approach, should a physician elect to

prescribe clonidine for hypertension pharmacogenetic testing could be used for assessing an altered risk score. There are two level 3 clinical annotations in PharmGKb related to the efficacy for treating liver cirrhosis in the alpha 2-adrenergic receptor (ADRA2C) and G-protein subunit beta 3 (GNB3) genes. While clonidine is an in vitro substrate for cytochrome P450 2D6 (CYP2D6) [16], the Royal Dutch Pharmacists Association released a statement finding that there is not a medically relevant drug-gene interaction despite the reported observation of decreased clearance in pregnancy [REF]. Together these reports suggest that from a pilot-centric approach to care management, the presiding flight surgeon may want to consider pharmacogenetic testing for ADRA2C, CYP2D6, and GNB3 in order to gain more patient-specific risk and efficacy information.

Conclusions

Diabetes, hypertension, and asthma affect military aviators across the range of military operations. There is a large amount of evidence supporting the use of genetics for tailoring medication to patients. Many medications for these conditions are considered safe with minimal aeromedical risk, such that an individual patient's risk profile will not elevate the overall risk above acceptable limits. However, we observed that for at least one medication, a patient's genetic profile may alter the efficacy or metabolism and thus required dosage and altered adverse effect frequencies. As a result, when prescribing these medications, we find that a physician would do well to consider pharmacogenetic testing to confirm a patient's individual risk level.

Abbreviations

ACE: Angiotensin converting enzyme; ADRB2: Beta-2-adrenergic receptor; CYP2C8: Cytochrome P450 2C8; CYP2C9: Cytochrome P450 2C9; CYP2D6: Cytochrome P450 2D6; EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; GLP1R: Glucagon-like peptide 1 receptor; G6PD: Glucose-6-phosphate dehydrogenase; PA: "Prudhomme approved"; a set of medications published by Prudhomme and colleagues; SD: Standard deviation; UAL: Upper allowable limit; UCL: Upper control limit.

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Author contributions

JLK scored side effects for severity, coordinated additional flight surgeons side effect scoring, collated side effect risk scores, and co-wrote the aeromedical aspects of the manuscript. JC collected pharmacogenetic recommendations for each medication, collated pharmacogenetic information into a database, and co-wrote the manuscript. CET interpreted the pharmacogenetic data and co-wrote the pharmacogenetic aspects of the manuscript. RRC designed the study, secured intramural funding, directed side effect collection and scoring, performed the statistical analyses, directed the collection of the pharmacogenetic information, and wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interest.

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