Medication Adverse Reaction, Risk Stratification (MAR^2S) Model

Corey M. Cronrath; Matthew P. Klick; Chad M. Merfeld; Steven J. Gaydos

BACKGROUND: A fundamental responsibility of aerospace medicine is the analysis and mitigation of the human component's risk to the aviation system. Medications are part of this risk mitigation process and are present within a multitude of work environments, including aviation. For example, during fiscal year (FY) 2013–2015, the Army Aeromedical Activity (AAMA) received 8596 medication waiver requests. During this same time period the U.S. Army Medical Department's Patient Administration Systems and Biostatistics Activity reported the organization prescribed over 187,668 prescriptions for opioids, 133,475 prescriptions for SSRIs, 116,649 prescriptions for muscle relaxants, and 71,723 prescriptions for hypnotics to its active duty soldiers in the outpatient setting.

METHODS: A conceptual model to mitigate the risk of adverse reactions to medications by severity score was developed based off the methodology published by Prudhomme et al.

RESULTS: The mean severity score of the 50 historically safe medications in the Army aviation community is 7346. The standard deviation of the population is 7300. The difference between safe and unsafe drugs determined by subject matter experts (SME) is highly significant when tested with the nonparametric Wilcoxon rank sum test.

CONCLUSION: The visual representation of the data from this conceptual model clearly demonstrates room for improvement from current methods. Historically, utilizing SME opinion has created a system with deficiencies related to high variance, inconsistencies, and perceived ambiguity. There is need for a model addressing adverse drug reactions that has concrete strengths of transparency, simplicity, and speed of use.

KEYWORDS: medication risk stratification, medication approval, aviation medicine, occupational medicine, workplace injury, prevention, decision matrix, medications.

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Benefit payments under workers' compensation programs totaled $61.9 billion in the United States for 2015.[13] Along with this, America's labor force is aging. The number of persons working past the age of 55 is at a historic high and, with 10,000 Baby Boomers (born between 1946–1965) turning 65 every day, understanding the implications of the growth and diversification of the aging labor force is becoming increasingly important.[14] According to the Bureau of Labor Statistics, the number of individuals ages 55 and above in the labor force will grow from 42.1 million in 2016 to 65.7 million in 2026.[3] It is known that the aging workforce will increase the prevalence in the workplace environment of health conditions and the medications used to treat them.[8] Yet, research evidence on the occupational injury risks from many common health problems and/or their treatments is limited.[3] A systematic review of the literature suggests a correlation of moderate increased risk of workplace injuries with medication use, although not wholly consistent.[6,10]

The U.S. Army, while not being affected by the aging workforce, may have the most to gain from a reduction in workplace injuries. Readiness is the number one priority of the Army since reducing its force strength from 508,210 in 2014 to 474,944 in 2018.[5] As an organization it cannot afford to lose its most valuable resource to potentially preventable injuries. From fiscal

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year (FY) 2013–2015, the U.S. Army incurred 9004 accidents resulting in cost of property or damage greater than $50,000 and/or an injury resulting in days away from work.[2] A total of 373 fatalities resulted from these accidents.[2] While further analysis of the diversity of the population is not readily available to these authors, it does highlight the need for further improvement in Army safety programs. During this same time period the U.S. Army Medical Department's Patient Administration Systems and Biostatistics Activity reported the organization prescribed over 187,668 prescriptions for opioids, 133,475 prescriptions for SSRIs, 116,649 prescriptions for muscle relaxants, and 71,723 prescriptions for hypnotics to its active duty soldiers in the outpatient setting.

A fundamental responsibility of aerospace medicine is the analysis and mitigation of the human component's risk to the aviation system.[12] Medications are part of this risk mitigation process and are present within U.S. Army aviation. During FY 2013–2015, the Army Aeromedical Activity (AAMA) received 8596 medication waiver requests for soldiers on flight status.

Occupational medicine providers have an obligation to protect workers and the organizations that employ them. For instance, 5147 fatal work injuries were recorded in the United States during 2017 and deaths from fatal falls were at their highest level in the 26-yr history of the Census of Fatal Occupational Injuries with 887 in 2017.[4] A systematic literature review suggests that some chronic health conditions and their treatments may raise the risks of occupational injury to a moderate degree.[10] Several studies have highlighted the poor knowledge that exists concerning the effects of prescribed medication on work performance.[7,9,11]

Therefore, it would be prudent for the community to investigate the possibility that medication use is contributing to preventable injuries in the workforce. Prudhomme et al. postulated a method to risk stratify the adverse reactions of medications on concepts from evidence-based medicine, systems theory, and risk assessment to accept or reject medications for use in the flight environment.[12] The Medication Adverse Reaction, Risk Stratification (MAR²S) model was built on this concept and uses a flight-centric approach, but may be altered to fit a wide variety of workplace environments. This conceptual model suggests that the MAR²S tool may reduce workplace injuries by using an evidence-based approach to stratify the risk of medications in the workplace.

METHODS

The authors utilized Prudhomme et al.'s[12] methodology below.

Step 1. Determine the sample for historically safe medications. The AAMA has published aeromedical policy letters to outline U.S. Army aviation's acceptable risk tolerance. The aeromedical policy letters classify medications and classes of medications into four categories. Selected from class one and two,[1] there were 85 medications generally considered safe for flight operations. Due to lack of published prevalence data, 35 were excluded.

Step 2. Identify all published adverse reactions of each medication. Lexicomp,[15] a reliable open-source database, provided published adverse reactions and prevalence data. Using Lexicomp standardized the evidence-based approach to identifying published adverse reactions for the MAR²S model.

Step 3. Assign a severity multiplier to each reaction based on recognized aeromedical concerns. A logarithmic scale was used to assign the severity multiplier to each adverse reaction.

Step 4. Develop a standardized protocol to establish the probability of adverse reactions. Lexicomp provided prevalence data for the MAR²S model. Occasionally Lexicomp publishes reference ranges for prevalence data for adverse reactions. For these reported cases, the prevalence score was calculated using the arithmetic mean for the range. An additional challenge during step 4 was some reported cases for adverse reactions did not have prevalence data due to limitations during FDA trials. In an effort to standardize the approach, for any prevalence data $< 2\%$ prevalence a score of zero was used.

Step 5. Calculate risk scores for reference medications. The medication scores for the reference medications were calculated using two formulas. The first assigns a severity score for each published adverse drug reaction (ADR) to each specific drug. In an effort to account for the entire side effect profile risk of a single medication, the second formula calculates an overall medication severity score by summation.

Step 6. Generate acceptance control chart. After summing the historically safe medications' severity scores, the mean was calculated, representing a quantification of the average risk in medication use historically accepted by U.S. Army aviation. The upper acceptance limit (UAL) and upper control limit (UCL) were determined using +1.5 SD and +3 SD, respectively. This technique was borrowed from lean six sigma literature and slightly altered by Prudhomme et al. The UAL and UCL were not plotted due to the high variance and over-inflation of these values. These values are recorded in the Results section.

Step 7. Utilize chart to assess medications of interest to aeromedical concerns. All medications with severity scores above the UCL suggest that they are unsafe for the workplace environment. Conversely, all medications with severity scores below the UAL suggest that they are safe for the workplace environment. Medications with severity scores that fall in between the UAL and UCL will need to be evaluated on a case by case basis. More research is required to control for the variance before this step can be used.

Four Occupational Medicine physicians used a consensus review board to assign severity multipliers (**Fig. 1**) to each adverse reaction. The completed database was submitted to the AAMA working group. The AAMA working group was comprised of five senior master flight surgeons from AAMA and the U.S. Army School of Aviation Medicine. The AAMA

Logarithmic scale	
Totally incapacitating (seizure)	1000
Partially incapacitating (drowsiness)	100
Distracting (heartburn)	10
Mildly distracting (dry mouth)	1
No occupational consequence (Decreased libido)	0

Fig. 1. Logarithmic scale assignment for individual adverse reactions associated with medications.

working group is considered to be the subject matter experts (SME) for Army aviation medicine. This step in the MAR²S is the crux of the model, allowing for flexibility to any community [e.g., Department of Transportation, Federal Aviation Administration, Department of Labor, mining and manufacturing industries, etc.] to allow subject matter experts to remain at the center of the risk mitigation process.

For drug "d" and ADR "a" (one of "*N*" total ADRs), calculate:

1. (ADR severity score) d, $a = (ADR\ prevalence)d, a \times (ADR\ severity\ code)a$; and
2. (Medication severity score) $d = \sum_{a=1}^{n} (ADR\ severity\ code)d, a$

RESULTS

The difference between safe and unsafe drugs is highly significant ($P < 0.001$) when tested with the nonparametric Wilcoxon rank sum test. The mean severity score of the 50 historically safe medications in the Army aviation community is 7492 compared to a mean of 9990 for unsafe medications (see **Fig. 2**). The standard deviation of the historically safe medications population is 7300. The upper acceptance limit severity score is 18,443. The upper control limit severity score is 29,394.

DISCUSSION

Overall the SMEs are consistent when comparing medications as a whole or by ADRs. The visual representation of the data from this conceptual model clearly demonstrates room for improvement. Of the 35 unsafe medications, 7 fall under the mean for the safe medications. For example, per SME in the Army aviation community, sumatriptan, with a severity score of 45, is deemed unsafe as a medication for flight and requires a waiver. This conceptual model using SME's opinion on the risk of individual ADRs suggests that sumatriptan is one of the safest medications in the aviation community. Conversely, diclofenac, severity score 29,753, is deemed safe for flight as a medication. The Federal Aviation Administration also has fallen into this conundrum. Migraine conditions aeromedical examiners can issue state that nonsteroidal anti-inflammatory drugs such as diclofenac require no grounding period, while abortive therapy with triptans, including sumatriptan, require 24 h of grounding.

This model is not without limitations. It does not have the ability to evaluate the synergistic events of multiple medications used by the same individual. Nor does it have the ability to evaluate adverse reactions of a medication based off dosage. The model does not take into account that the larger the population of people using a medication, the more adverse reactions there will be in the workplace, even rare severe ones. Issues of preexisting conditions and atmospherics changes are other factors not accounted for by the model, making it impossible for the model to be a standalone decision matrix.

Traditionally, trial periods of medications are used to evaluate adverse reactions of medications. The authors believe self-reporting is a less than an optimal technique in situations where secondary gain is plausible. In addition to this, the model is not validated by research. Although, it is plausible that utilization of this risk mitigation process will decrease workplace accidents and injuries.

While the model incorporates objective data points into the subjective process of determining safe and unsafe medications in the workplace, it is still reliant on SMEs. This is both a strength and a weakness. Concrete strengths of the MAR²S model include transparency, simplicity, and speed of use. This model can calculate a new medications severity score within 5 min, thus giving the MAR²S model the capability of keeping up with the rapid development of new medications in this era. The model is standardized and can easily be understood, eliminating the perception of being arbitrary and capricious. Most importantly, it is flexible and can be adapted to a rapidly changing work environment. These strengths address the gaps of the current SME opinion model in use today.

The intent of this model is to offer subject matter experts an additional data point. It is not meant to be a standalone decision matrix. Risk mitigation of medications in the workplace is a complex endeavor that requires careful consideration of multiple variables and data points that only the human being is capable of effectively analyzing. Therefore, SMEs need to be the final decision point. The authors suggest that transition to a more methodical and transparent system is a better approach than methods currently employed by many organizations.

In order to further increase transparency and logic imbedded within the model, the authors recommend studies aimed at accurately identifying the symptoms of a 0.04 blood alcohol level in a manner consistent with how adverse reactions of medications are identified. With this knowledge, alcohol could be used within the model as the severity score at which impairment occurs or a medication is deemed unsafe. This would keep the model aligned with current Department of Transportation punitive measures for intoxication at work.

Prospective randomized trials are required to evaluate the efficacy of the MAR²S model before use. If these trials suggest that the model decreases workplace accidents/injuries, then the model will begin to transition from a theoretical concept to a validated tool.

Organizations should consistently strive for improvement regarding risk identification. The use of the MAR²S model has the potential to be a single data point among many in order to make the determination of safety in the work environment.

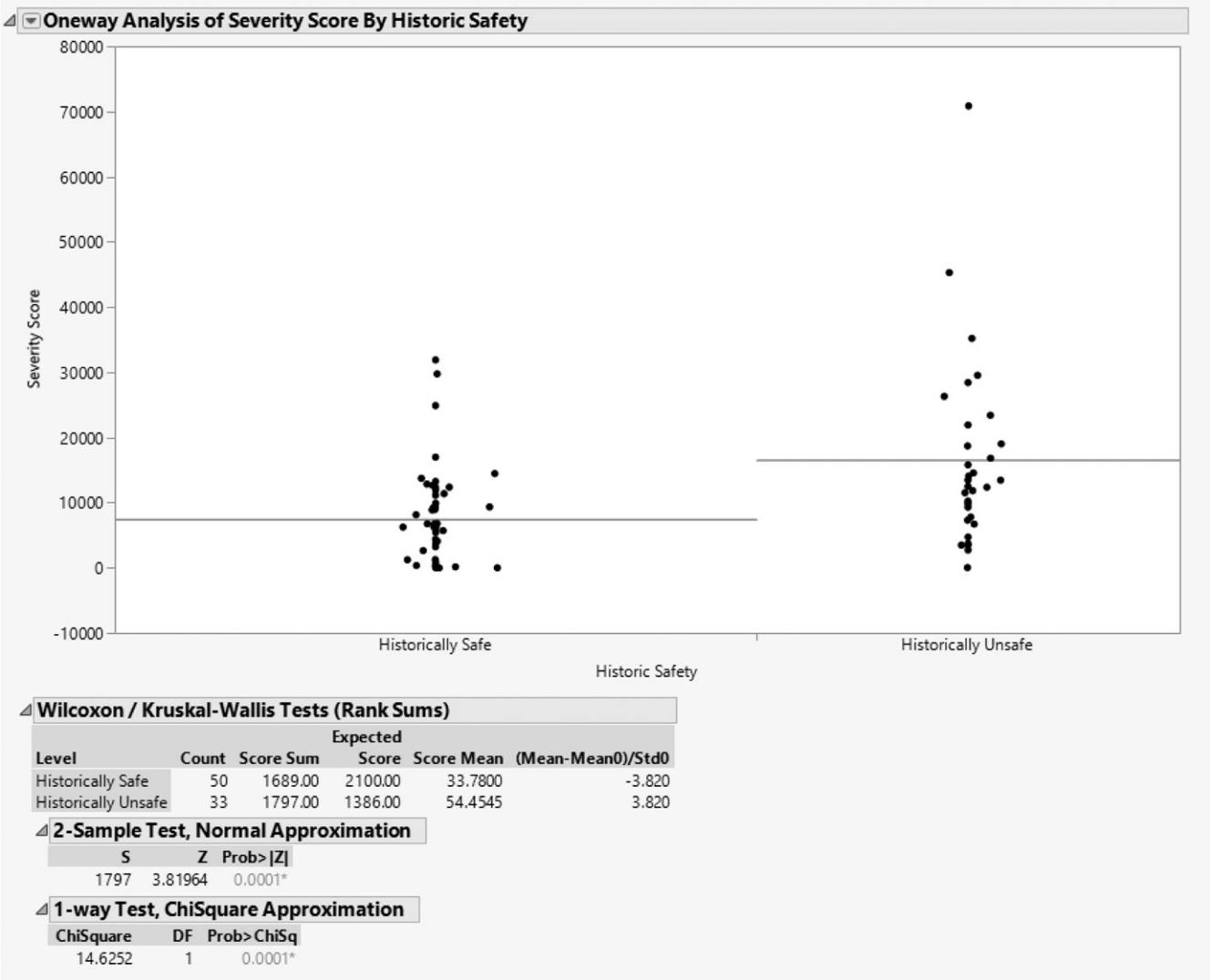

Fig. 2. Historically safe medications with a mean severity score (gray line) of 7492 plotted on the left. Historically unsafe medications with a mean severity score (gray line) of 9990 plotted on the right.

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