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LETTER FROM THE EDITOR

Dear Readers:

Welcome to another issue of ReFlections. This edition contains two articles I hope will stimulate your interest and further your knowledge. The first article is written by Dr. Sharylee Barnes. It provides valuable insight into sleep apnea, a common diagnosis noted during the process of underwriting. Dr. Barnes discusses in detail the complexity of this condition and its impact on mortality. The second article deals with the use of pharmacy checks. In this article, I discuss both the benefits and potential risks of utilizing easily obtainable prescription records during the underwriting process.

I hope you enjoy both of these articles.

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SLEEP AND SLEEP APNEA

By Sharylee Barnes M.D., D.B.I.M.

Breathing Ventilation

Sleep apnea, ordinary sleep and breathing are fascinating physiologic processes. One needs to better understand sleep and ventilation in order to understand its disorders which encompass much more than Obstructive Sleep Apnea (OSA) and continuous positive airway pressure (CPAP).

OSA is a familiar underwriting problem where knowledge about normal sleep/wake physiology is helpful. Central Sleep Apnea (CSA), on the other hand, is an infrequent challenge for underwriters; it is difficult to diagnose clinically and is overlooked in the medical literature. CSA is a very serious condition with significant mortality risk.

This article describes the relationship between the various types of sleep apnea and mortality risk, as well as provides a brief overview of sleep medicine literature.

The action of breathing depends on a very complex feedback control system in which the brain organizes neuromuscular output to the respiratory muscles of the upper airway, the chest wall, diaphragm and lungs. The response of the airway, chest wall and lungs to impulses from the brain alters the arterial blood concentrations of oxygen and carbon dioxide, and consequently affects acid-base balance (pH). Specialized sensors, located in the carotid arteries and throughout the respiratory system from the oropharynx to the diaphragm monitor the rate of gas exchange and send impulses back to the brain which in turn adjusts and regulates the system. The hypercapnic-apneic threshold is an extremely important trigger to initiate brain ventilatory output. This threshold depends on the responsiveness of the sensors and brain to the partial pressure of carbon dioxide in the blood (PaCO2). A simplification would be: how high does the carbon dioxide level have to become to trigger a breath?

Oxygen saturation (O2Sat), the amount of oxygen being carried in the red blood cells, is measured as the percentage of the hemoglobin in the red cells that is carrying oxygen. Another measure of oxygen is the partial pressure of oxygen in the blood (PaO2). When either one is low, the terms hypoxemia (low oxygen in the blood) or hypoxia (low oxygen) can be used. The terms are used almost as synonyms, though their actual definitions vary.

Precise knowledge of how sleep/wake physiology works is not really needed for insurance underwriting, but an appreciation of its complexity may help with understanding sleep studies and their limitations. There are two principle stages of sleep: non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM).

Extremely rich feedback systems take place among myriad sensors, receptors, hormones, the autonomic nervous

system, the brain and anatomic structures. Some of the anatomic features listed below illustrate the complexity of sleep/wake physiology:

- cholinergic neurons
- brain stem
- hypothalamus – preoptic area
- forebrain – basal area
- medulla – solitary nucleus region
- thalamus – reticular nucleus
- locus coeruleus
- muscles of throat, rib cage, diaphragm, etc.
- dorsal pontine descending axons
- carotid bodies (specialized cells sense PaO2 and PaCO2)

In normal sleep physiology all the above features and others participate in feedback loops to produce NREM and REM sleep stages. NREM goes from light sleep to deep sleep in another four stages. Normal REM sleep characteristically has swings of blood pressure, heart rate, irregular respiration and, interestingly, a few periods of apnea or hyponea. There is loss of muscle tone (paralysis) in REM sleep, but the brain's electrical activity in this stage is high, similar to wake activity when measured on an EEG. Body temperature and certain hormone levels such as cortisol, thyroid-stimulating hormone and melatonin are designed to fluctuate during sleep. The proportion of NREM to REM sleep varies from cycle to cycle with the most REM at the end of the sleep period. The anatomy, feedback loops, hormones, muscle tone, sleep stages and swings in autonomic regulation all contribute to the intricate physiologic balance.

Cardiovascular Physiology in Sleep

The cardiovascular system responds to gas exchange, apneas, hyponeas and sleep interruptions. Normally there is a lessening of sympathetic tone and an increase of parasympathetic tone – changes that mean lower heart rate, blood pressure and cardiac output. These changes produce a diminished cardiac workload and a lower oxygen demand which results in an environment that provokes fewer arrhythmias. Therefore sleep is thought to be cardio-protective. It seems logical that many arousals from sleep due to sleep apnea would cause a loss of this presumed benefit.

Gradual awakening is different from abrupt arousal from noise or sleep apnea. The latter causes a surge in sympathetic tone with its resultant increase in heart rate, blood pressure and respiration. Sympathetic tone also varies, perhaps less abruptly, in normal REM sleep.

These facts drive many theories about the possible harm of sleep apnea which by its nature is repetitive and long term. These theories include oxidative stress or sympathetic stress, but it must be remembered that REM sleep has episodes very similar to awakening from OSA.

Apneas

OSA means there is normal respiratory effort with cessation of airflow during sleep. Central Sleep Apnea (CSA) means there is simply no effort to breathe. Mixed Sleep Apnea usually has an initial period of CSA followed by OSA.

The definition of hypopnea is that there is a breath with half the respiratory volume of the adjacent breath combined with either arousal or oxygen desaturation of 3-4% or more. To be part of a sleep syndrome, episodes of apnea or hyponea must last 10-15 seconds and occur five or more times per hour.

Healthy people may have any type of apnea at sleep onset or during REM sleep, but the episodes are short and not repetitive. Usually they don't cause arousal or a change in type or stage of sleep. Occasional longer periods of apnea (30 seconds or more) can occur in normal people without arousal.

Frequency of Sleep Apnea in the U.S. Male Population

One measure (index) of the degree of sleep apnea is the apnea/hypopnea index (AHI), which is the sum of the number of apneas plus hypopneas during a whole sleep study divided by the hours of the study. This gives the number of apneas and hypopneas per hour, the AHI.

If sleep apnea is defined as an AHI > 5 (a popular definition), some U.S. figures show that 27% to 35% of men qualify. However, many of those men have no clinical illness. If the definition includes an AHI > 5 and daytime sleepiness or hypertension, 9% of U.S. men fit the definition.[35] The incidence of sleep apnea increases with age, particularly after age 50, but even in 50-year-old males a 9% frequency in this population seems far higher than common sense would accept. Other figures state that the incidence in non-obese populations is only 3%.

Sleep Deprivation Symptoms

Below is a list of sleep-deprived symptoms. Most people will experience these symptoms at some time to a small degree:

- fatigue
- hypersomnolence
- decreased concentration
- forgetfulness
- irritability
- anxiety, depression
- muscle ache
- impaired cognition
- impaired motor skills
- morning headache
- mistakes, accidents

Sleep deprivation can be caused from simply not going to bed on time to having some type of sleep apnea or a variety of other factors.

Some conditions have been confused with apneas or their symptoms. Circadian rhythm disorders exist when the internal circadian rhythm is not synchronized with external time such as in jet lag, shift work or delayed or advanced sleep-phase syndrome. Narcolepsy is not sleep apnea. It is a condition where sleep attacks occur with cataplexy (transient loss muscle tone). Narcolepsy tends to be life-long. However, it is well treated with medications like modafinil and amphetamines. A current theory is that a deficiency of hypocretin (orexin) in the lateral hypothalamus of the brain is the actual cause of narcolepsy.

Central Sleep Apnea

There is symptom overlap between sleep deprivation and Central Sleep Apnea (CSA), too, but some things are more particular to CSA such as lethargy and dependent edema. CSA patients may or may not complain of shortness of breath even though oxygen levels are low. They may have physical findings of cyanosis and evidence of right-sided heart failure. Secondary erythrocytosis or polycythemia is common.

Causes of CSA

There are several medical conditions which can secondarily cause CSA. The single most common presentation of a form of CSA is in heart failure patients. They develop a Cheyne-Stokes breathing pattern and some say this is the cause of 25% of all the cases of CSA. People with these two problems are not likely to be insurance applicants. Other causative conditions include:

- Stroke, TIA, MS, traumatic brain injury, epilepsy, congenital brain injury or malformation, Arnold-Chiari associated mid-brain anomaly, meningitis, encephalitis, neurodegenerative disorder; basically any organic brain disorder or upper spinal cord injury
- medications, alcohol, substance abuse, anesthesia
- high altitude periodic breathing (mountain climbers)
- metabolic alkalosis PaO2/PaCO2/ pH out of balance
- afferent neuron damage in cervical spinal cord disease
- hypercapnea (due to low alveolar ventilation)
- Ondine's Curse (exceptionally rare), also called Congenital Central Hypoventilation Syndrome (respiratory arrest during sleep due to a failure of autonomic control of breathing)

Cheyne-Stokes Respiration (CSR), as mentioned above with congestive failure and in high altitude breathing, is marked by a crescendo-decrescendo pattern of breaths, followed by central apneas or central hypopneas, some lasting as long as 30 to 40 seconds. Those with CSR are often hypocapnic (low CO2) during wakefulness. Other conditions that can promote CSR at normal altitude include hypoxia, decreased lung volume, decreased metabolic rate, renal failure and possibly cerebrovascular disease.

CSR in healthy persons at high altitudes starts with hypoxia stimulating more breathing (hyperventilating) and resulting in hypocapnia (because CO2 is blown off). The complex chemo reflex feed-back loops are disturbed.

Obstructive Sleep Apnea

Some symptoms overlap between sleep deprivation and Obstructive Sleep Apnea (OSA), but some are more particular to OSA, including very loud snoring, cessation of breathing, choking, sitting up and fighting for breath, abnormal movements, thrashing in bed, nocturia and sweating.

The differential diagnosis of symptoms common in OSA is quite wide. The possible diagnoses include: insomnia, simple sleep deprivation, asthma, cardiac disease, neurodegenerative disorders, brain tumor, drug or alcohol overuse, psychiatric disorders, allergic rhinitis or sinusitis with excessive mucous, and impaired swallowing (laryngeal nerve paralysis), along with the usual causes of OSA described later in this article. Physicians have to consider all these diagnoses when deciding whether to order a polysomnograpy or overnight oxygen monitor, and when interpreting the sleep studies.

Causes of OSA

Obstructed airway during sleep can be caused by several things. Obesity is thought to contribute to about 70% of cases. Having a small or crowded oropharynx, often seen with a short neck, predisposes to obstructing the airway. If the muscle tone of the oropharyngeal muscles is inadequate due to improper central control, medications or alcohol, the passages will not be held open. Excess negative intrathoracic pressure produced by efforts of the chest wall and diaphragm can cause full or partial collapse of the upper airway. If the bony and cartilaginous support of the upper airway is less than normal, obstruction may occur. The airway can be encroached upon by an anatomic disorder, from malformation of the face or dentition or by a tumor.

Other Sleep Apneas

A few conditions are associated with both OSA and CSA. Most of them are fairly uncommon and the association with apnea for each diagnosis is even less common. They include: Pickwickian Syndrome, hypothyrodism, renal failure and acromegaly. Pickwickian Syndrome is defined as hypoxia and hypercapnea during sleep in a very obese person. The exact cause is unknown, though it is thought to be a combination of CSA and excessive weight against the chest wall preventing chest wall movement which restricts ventilation. An obese person can also have simple OSA, so the combination of obesity and sleep apnea alone does not make the diagnosis of Pickwickian Syndrome.

Overview of Sleep Medicine Literature

The relatively new discipline of sleep medicine has produced a large body of medical literature. There is an association between OSA and early mortality, so much of the literature attempts to analyze the nature and significance of the association. A major paper in 2007 in the journal Sleep was written by three Mayo Clinic authors who produced an extensive and careful review of the published theories, observations and associations concerning sleep disorders. [21] They analyzed 160 references touching on many different aspects of OSA (about 50 hypotheses). Some of the theories are described below:

Sympathetic nervous system activity causes temporary blood pressure increases during obstructive apneic events. A theory is that people with OSA have this nervous system response in an exaggerated way that lasts beyond the apneic events. Or put differently, people with OSA have an elevated sympathetic tone that carries over into the day causing hypertension.

Normally lung inflation activates stretch receptors in the lung and chest wall that are partly controlled by the Vagus nerve. Incomplete pulmonary inflation in OSA might interfere with this reflex and thereby interfere with homeostasis.

Repetitive reoxygenation after OSA events is thought to cause “oxidative stress” affecting mitochondrial function, though authors of these papers say it’s hard to separate that stress from that of the simple low oxygen level that precedes it. [1, 10, 14] Awakening due to OSA does cause abrupt increased sympathetic tone, blood pressure and heart rate, but so does awakening by noise. An experiment on dogs showed that those with OSA plus noise awakenings compared to dogs with noise awakening alone both had higher daytime blood pressure.

The Mayo analysts point out that OSA is very often accompanied by aging, obesity, metabolic syndrome, diabetes and hypertension, all strong cardiovascular risk factors. In the new field of sleep medicine, randomized interventional trials or long-term cohort studies are not available. This makes it next to impossible to assess the independent effect of OSA on cardiovascular risk (if any) compared to the effect of the common co-morbid conditions on that or any risk. In 2008, the American Heart Association

(AHA) and the American College of Cardiology Foundation (ACCF) issued the following joint scientific statement: "Because all these conditions are chronic, have multifactorial and overlapping origins, and have long latent periods before symptoms appear, identifying a causal role of OSA is difficult." [6]

The Mayo authors state that sleep medicine literature so far is principally made up of case-control studies able to generate hypotheses on new possible physiologic mechanisms, but thus far there are biases and conflicting results. Most studies use the AHI as the measurement of severity of OSA and leave out the potentially more important measures of degree and/or duration of low oxygen saturation.

The Mayo authors stated that conflicting data do or do not support the theory that OSA leads to enhanced sympathetic tone because of an exaggerated chemoreceptor response to hypoxia. [5, 7, 9, 2, 12]

My observation is that some of the studies involved only one or two nights of continuous positive airway pressure (CPAP) and most involved less than six months of treatment. The larger trials have surprisingly few subjects. Frequently there are less than 50 individuals in a published study and only a handful of trials have more than 600 individuals. [4,8] Many of the studies classed their severe group as having an AHI > 20, which would include many individuals that the insurance industry would class as mild to moderate OSA for risk assessment purposes.

The language used by the Mayo authors in their analysis is telling. Here is a partial list of the phrases they used to describe the conclusions possible from the 160+ studies available to them:

- "thought to be important…"
- "whether this results from….is not entirely clear …"
- "it is conceivable that…"
- "conflicting human and animal data …"
- "remains to be determined…"
- "does not clearly demonstrate…"
- "may thus contribute indirectly…"
- "can be difficult to decipher…"
- "seems to have…"
- "is unclear…"
- "difficult to disentangle its independent effects…"
- "vulnerable to hidden biases…"
- "studies have failed to demonstrate…"
- "have yielded conflicting results …"
- "could predispose…"

Dr. Sudhansu Chokroverty, a sleep medicine specialist at the New Jersey Neuroscience Institute at John F. Kennedy Medical Center and the Robert Wood Johnson Medical Center, has offered the following thoughtful conclusions about morbidity and mortality associated with OSA: "The mortality associated with sleep apnea is not yet well defined and limited new evidence suggests that treatment with CPAP reduces mortality." [25]

He notes there is a strong association between OSA and hypertension, stroke and a higher risk cardiovascular profile. [22, 23, 11] He also points out that Syndrome 'X' is a cluster of classic known cardiovascular risk factors — hypertension, obesity, diabetes and hyperlipidemia — and there is an association between Syndrome 'X' and OSA. He further states that some individuals want to add OSA to the syndrome and rename it Syndrome 'Z.' Chokroverty concludes, as do others, that the association between the classic cardiovascular risk factors and OSA makes it extremely difficult to prove whether OSA is an independent risk factor for cardiovascular disease. [17]

In July 2008 the AHA and the ACCF joint scientific statement, which was referenced earlier, had essentially the same conclusions that Dr Chokroverty published. The AHA and ACCF authors reviewed more than 600 papers from the medical literature before issuing their statement. Their review included hypertension, stroke, cardiovascular risk factors and death as end points in the various papers.

A few other studies do suggest the potential for OSA to be an independent risk factor for death in known cardiovascular diseased patients. The time of day at death for cardio-vascular system (CVS) patients with OSA is shown to be different than for CVS patients without apnea. [26] Deaths in patients with OSA tend to peak between midnight and 6 a.m. (presumably when individuals were asleep), while deaths in patients without OSA tend to be between 6 a.m. and noon.

No long-term studies with rigorous methodology and design exist to support the various hypotheses about the role of OSA in cardiovascular risk or death, or the potential effect of treatment of OSA on that risk.

We are left wondering whether there is anything certain about OSA. For underwriting purposes we can say that car accidents definitely increase with sleepiness. [27] OSA is strongly associated with traditional insurance risk factors, such as obesity, hypertension, diabetes, Syndrome X and hyperlipidemia. How much or whether OSA treated or untreated adds to the known risks is still uncertain. Overuse of alcohol also is associated with both OSA and mortality, and the combination is of concern for life underwriting. Additionally alcohol with excessive sleepiness could point to true Central Sleep Apnea and all three of these problems are independent mortality risks. It does seem clear that treatment with CPAP relieves the clinical symptoms of OSA, which can be very significant to an individual's quality of life and his or her productivity. [14, 10]

Medical literature on CSA is hard to find. The actual disorders that can cause CSA are the focus of most studies and that focus could explain the paucity of literature on CSA itself.

There is almost no data linking the results of polysomnography to CSA. One reference states that the percentage of central to total apneic events should be 80% in order to make the diagnosis of CSA. [17] One sleep study specialist said his sleep lab uses a minimum of 40% centrals to totals to make the diagnosis of CSA.

In underwriting it is doubtful that we will see true CSA without seeing one of the known causes of CSA in the medical records. Treatment of the cause is the best way to treat CSA. If the cause is untreatable, CPAP may offer relief of symptoms. Unfortunately many causes of CSA are not treatable and occur in patients who are obviously ill and uninsurable. Insurers would particularly wish to exclude the diagnosis of CSA when a sleep study was done or recommended on a person who also had a history suggestive of organic brain disorders, including closed head injury, stroke, epilepsy, MS or any of the other causes of CSA listed earlier in this article. For these people obtaining the actual polysomnography report is essential to underwriting.

Ventilation during sleep and its disorders are part of an emerging field of medicine that has produced both hope and controversy. Underwriting these complex problems is a challenge for our industry that can be addressed in a pragmatic way by considering the natural history of the disorders. The co-morbid conditions that often accompany or cause Obstructive, Central and Mixed sleep apneas are at least as important as the apnea itself. Experts have called for sleep medicine research to develop randomized large cohort studies over extensive time frames. ■

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PHARMACY CHECK UTILIZATION

By J. Carl Holowaty M.D., D.B.I.M

A fundamental aspect of medical risk selection is the ability of underwriters to ascertain the current and past health of the applicant. Medical information regarding the applicant can arrive in many forms, including an applicant's own statement of his or her health, medical records from attending physicians and treatment facilities, and laboratory/paramedical evaluation. In addition, coded data from the Medical Information Bureau (MIB) can provide an alert as to possible misrepresentation of medical history.

Just as medical information plays a vital part in risk selection, the use of pharmaceuticals forms the basis of much of the modern treatment of medical conditions by physicians. The ability to easily view an applicant's prescription history can substantially increase the confidence needed to accurately risk stratify. The purpose of this article is to illustrate the various uses of prescription database (PDB) information in order to discuss the value of this new underwriting tool. It is also to consider its possible impact on underwriting, claims adjudication, producers and consumers. The automation of gathering and displaying prescription histories may in some ways be considered as having the same impact as that of blood testing when it was first introduced to insurance procedures.

One purpose in viewing an applicant's medical history is to try to estimate the potential future course of the applicant's various medical conditions. In general, the aim of the underwriter is to learn of any past or current health conditions, estimate their level of severity, compliance with treatment and response to therapy. In fully underwritten cases, in addition to the applicant's own statement, this often involves collection of blood/urine specimens, paramedical evaluation, and sometimes one or more attending physician statements. The accuracy of the evaluation can be compromised by either deliberate or inadvertent means, such as material misrepresentation or a faulty memory. The ability to view an accurate record of a person's past and present use of prescribed medications may be considered as a reasonable surrogate of various health conditions, since many significant health conditions require pharmaceutical therapy. In a similar fashion to an MIB report, an accurate record of pharmacy records can provide a valuable alert to conditions and the identities of attending physicians that are not otherwise disclosed during the underwriting process.

The true value of the use of PDBs lies at least partially in their relative exclusivity from other sources of medical information. As an example, applicants may state they are in good health and do not have a regular physician. A PDB may reveal, however, they are receiving regular prescriptions for anti-hypertensive medications, possibly from more than one physician. The protective value in this situation may be significant, and unless the paramedical measured BP is abnormal, would be exclusive. If, however, a person has already disclosed they are being treated for hypertension, then the value of a 'hit' for anti-hypertensive medication is compromised, since it merely confirms what is already known through other forms of information gathering. What it does provide is a record of what drugs are taken, and it can be suggestive of when and how the medications are being used. This has some value of its own, since in chronic conditions such as hypertension, compliance with treatment is essential to the long-term maintenance of normal blood

pressure in order to reduce the sequelae of this condition. Without the knowledge that the PDB provides, at best we can only rely on paramedical exams and attending physicians' statements to know the recent blood pressure, as well as sporadic office blood pressure levels and the medications that were prescribed for the condition. As a former medical practitioner I was well aware of the general lack of compliance in getting patients to take prescribed medications for many conditions, including chronic conditions such as hypertension and diabetes. The PDB can be useful to suggest compliance with treatment.
Like any underwriting tool, the value of PDBs may be dependent on how they are used. For instance, if they are used as a screening tool in a population of fully underwritten young applicants relatively free of serious medical impairments, they might provide less value than when used in an older population with underwriting requirements that are less stringent. At older ages, the high prevalence of diseases and use of medications make the likelihood of meaningful 'hits' much higher. The face amount at risk, of course, would also be a consideration on determining the protective value.

Some of the considerations in realizing the value of PDBs lay in determining whether there is excess mortality associated with the use of any individual drug or classes of drugs, regardless of whether the treated condition is known. This links the associated mortality directly to the medication in question, rather than to a medical condition. This important concept will be examined in greater detail later in this article. Some of the results may be intuitive, but this is not always the case. For example, it may be anticipated that in the general population, favorable mortality would be expected in those applicants that don't require any prescription drugs, since the suggestion is that they are healthy. This is unfortunately not always the case. Within this group, there are those that are truly free of any conditions associated with excess mortality, but unfortunately there also are significant numbers of people with unrecognized and untreated common conditions such as hypertension and type 2 diabetes. There also may be people who have had conditions diagnosed, but for various reasons neglect to take prescribed drugs to treat them.

In order to determine the relative risk between these two groups, it is possible to actuarially 'mine' the death files from the Social Security register of deaths and compare this to the files of people who are being prescribed or have been prescribed most drugs over a sufficient time. Evaluating a large number of users lends greater credibility to the analysis. Owing to the very high numbers of people using the more commonly prescribed drugs, this credibility can be established with some accuracy. The methodology and results can be reviewed in detail in the recently recorded webcast provided by RGA's actuary, Tim Rozar, on http://www.rgare.com/underwritingconnection/.

The information gathered with this analysis of PDBs needs to be carefully considered. Several concerns come to mind. These include:

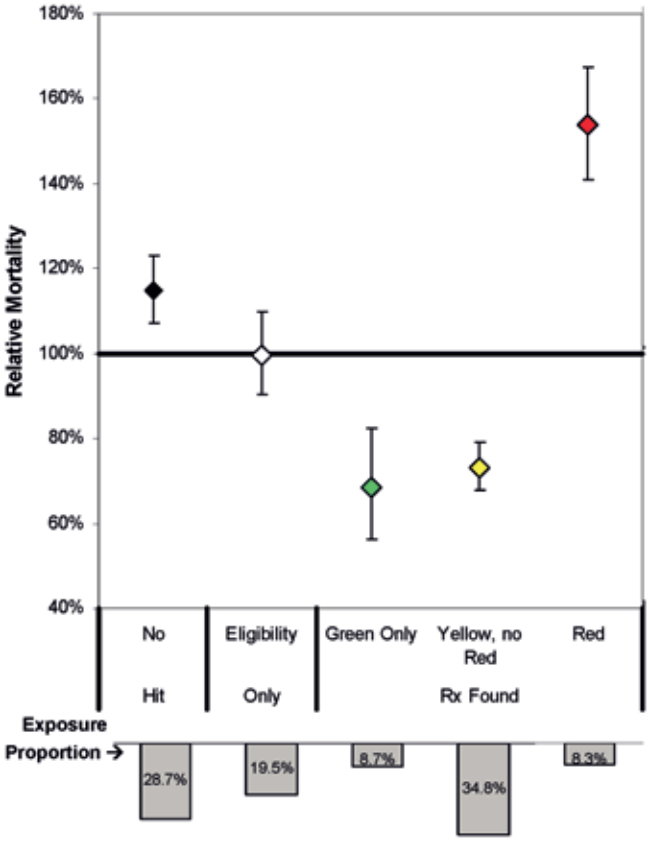
1. How thorough is the PDB in determining a person's prescription history?
2. How well is a drug's use correlated with particular conditions, and how far can one go in inferring the presence of disease states?
3. If a drug is associated with low mortality, or conversely high mortality, is it reasonable to act on that basis?
4. What are the most commonly used drugs, and is there sufficient evidence linking them to excess mortality to justify the cost of this tool?
5. Are there any unique legal or ethical considerations in using this information?
6. What is the value of PDBs when stratified by age, face amount or the type of insurance applied for (e.g. fully underwritten vs. simplified issue)?
7. Will there be a sentinel effect associated with the use of this tool, and will late adopters be prone to anti-selection?
8. If a drug or class of drugs is associated with excess mortality, can there be significant variation in the mortality based on a given individual, rather than a large group of individuals?
9. Is the mortality association of a particular combination of drugs greater than anticipated from a cumulative summation?
10. In the elderly, is there excess risk associated with the total number of drugs prescribed (e.g. Fatal Adverse Drug Reactions), regardless of how each individual drug is evaluated?
11. How will the use of PDBs affect ordering patterns for other underwriting requirements?

The remainder of this article will deal with a commentary on these questions. Some of the information is quoted from the webcast slides from RGA's recent presentation developed jointly by our own actuaries and Intelliscript.

At present, there is approximately a 75% likelihood that a request for a PDB check on an insurance applicant will result in a 'hit.' This includes people who are qualified for health care plans, regardless of whether they have taken any prescribed medications during the period in question. This is an average number, since there can be some variation

depending on face amounts and age bands. The absence of a hit can, in general, have mortality implications of its own, since some of these applicants may have inadequate access to health assessment and treatment. The comparative mortality of this group is demonstrated in the graph below.

Mortality Study Results*



***Drug Risk Hierarchy**

Each drug is classified as Red, Yellow or Green to indicate the relative mortality (or morbidity) risk of impairments associated with each drug.

Assignment of drugs performed prior to and without knowledge of mortality study results.

Mortality study groups are divided as follows: Green Only; Yellow, No Red (with or without Green); and Red (with or without Green and Yellow).

Data supplied by Milliman-IntelliScript

Each drug assessed in a PDB has conditions for which it is commonly prescribed, as well as some conditions for which it may be used in an 'off-label' fashion. Although the work done by RGA and Intelliscript shows the association between a particular drug (or class of drugs) and mortality, the study essentially ignores the specific condition(s) for which the drug can be used. As such, the excess mortality represents the aggregate mortality of all of the prescribed conditions. As an example, some widely prescribed beta-blockers are commonly used to treat hypertension. It is not unusual, however, to see this same type of drug used to treat such disparate conditions as cardiac arrhythmias, congestive heart failure or essential tremor. The mortality associated with each of these conditions (as opposed to the mortality associated solely with the medication use) will show considerable variation. In this case, applying an aggregate mortality to an individual case could result in inaccuracy in the rating assignment, as well as unfairness to some of the applicants. The risks to the insurer in neglecting this consideration include 'business lost,' as well as inappropriately low rates for serious illnesses.

It is not nearly as easy as one might think to determine which are the most commonly prescribed drugs. Different source lists provide less than ideal concordance. Some rankings are based on the total number of prescriptions written while others are based on the number of pills that are prescribed. The rankings can change significantly from year to year as well, since it is not uncommon for drugs to be removed from circulation due to health concerns, and new drugs can jump high up on the list if they are well marketed and shown to be beneficial. However, review of several sources suggests that certain classes of drugs consistently rank highly. These include drugs used to treat pain, anti-biotics, lipid-lowering agents, anti-hypertensives, anti-asthmatics, thyroid replacement drugs and anti-depressants.

As insurers, it is accepted that we can discriminate on the basis of a person's health history and current conditions if we can show studies that document excess mortality or if there is a reasonable expectation of excess mortality. Our mortality studies have shown an association between prescription drug history and mortality. There is obviously a link between prescription history and medical history. But how reliable is it? And how acceptable will this link be in facing up to legal or ethical challenges if it is used as the sole determinant of a rating decision? As I illustrated in the paragraph above, there are some dangers in using prescription drugs histories as a direct surrogate of specific conditions since there may be considerable variation on a case by case basis. This is important, since challenges to the use of PDBs may come on a case by case basis, and fairness and equity can be challenged if the details are not fully developed in the underwriting process.

At present, a signed medical authorization on an insurance applicant legally allows us to perform a PDB inquiry. The law also protects applicants in that they are allowed to contest the accuracy of the record. It is not clear yet, however, how

the insured population will view our use of their records, especially since public awareness of this tool probably still remains low. It will be important to develop public relations guidelines to manage inquiries on this subject in the same manner that the issue of blood testing was managed in the past. It also will be important to be prepared to handle the inevitable contesting of decisions that were made primarily based on medication use without any confirmation of the treatable condition.

As mentioned earlier in this article, a great deal of the protective value of PDBs may lie in their exclusivity from other sources. Intuitively the greatest exclusivity would occur in cases where underwriting data is limited, such as simplified issue cases. This would be magnified if those same cases are for high face amounts, as well as in populations such as the elderly who have a high prevalence of treatable conditions. While the use of this tool in such a population would yield high exclusivity, the risk of doing less than full underwriting would be fraught with risk. On the other hand, if it were used in young populations for low face amounts, it would be similarly exclusive, but the prevalence of high mortality conditions would lower the yield rate of 'hits.' Obviously, there is a need to determine the balance points between all of these considerations. Estimating the value of this type of tool will need to be determined by the type of product, age ranges, face amounts and, of course, how it is used in relation to any other traditional underwriting tools. This will present similar actuarial pricing challenges in the same way that integrating blood testing and preferred criteria has done in the past.

There is a reasonable expectation that using PDB checks, if done as an adjunct screening tool rather than a replacement for traditional risk methods, will result in more underwriting accuracy and possibly less misrepresentation, especially as the public becomes aware of this powerful new confirmatory risk evaluation tool. As with any new significant tool, there is a risk that a dichotomy may quickly develop between the early adopters and the late adopters. As applicants and agents learn of this tool and develop knowledge of who is using it, there may be a tendency for late adopters to experience worsening mortality results if they are exposed to increasing levels of anti-selection.

Currently, the analysis of mortality associated with prescription drugs is in its early phases. While commonly prescribed drugs can be easily evaluated on an individual basis, more work needs to be done. Polypharmacy is quite common in treating various conditions. For example, the combination of anti-hypertensives, anti-hypercholesterol drugs and anti-hyperglycemics is common, and the effects of the concomitant use of multiple classes may present some surprises. RGA/Intelliscripts mortality study suggested that there is a mortality benefit at least in some cases to being on certain drugs. We do not yet know if this beneficial effect starts to change as the total number of drugs increases. In an earlier edition of Reflections, I reviewed the topic of Fatal Adverse Drug Reactions (FADR). In the article, I illustrated the association between the total number of prescription drugs and the not inconsequential risk of FADRs. Since polypharmacy is disproportionably prevalent in the elderly (along with serious multiple health conditions), the study of drug combinations will be important.

Another area for further investigation is the pattern of drug use, both for individual medications and multiple medications. For example, oral narcotics are associated with excess mortality; however there may be considerable variation depending on the frequency and pattern of use. A person who has used narcotics once in the past in relation to a dental procedure will likely have quite different mortality than someone who is continually on the same drug and who has used them in large quantities possibly from multiple physicians. The use of customary underwriter judgment will certainly recognize these differences, assuming the case decisions are reviewed by underwriters with adequate experience.

Since the information available from PDB checks can be considered to constitute at least a partial surrogate for medical conditions or disease states, there may be a tendency to order them in an effort to reduce the number of Attending Physician Statements (APS). While APSs are costly, both in time and money, the information and protective value they provide is very high, when ordered selectively. A PDB should not be considered to be a direct substitute for this level of protective value. In its simplest terms, the PDB can 'hint' at the presence of suspected medical conditions, but would be of little use in estimating the severity of the condition. Likewise, it may suggest a certain degree of compliance with pharmacotherapy, but it can't confirm control. Conditions such as diabetes or hypertension are two common examples where medical compliance is critical, but does not ensure control. Just as the use of PDBs may not safely reduce the need for APSs, it is possibly more likely that they will in fact raise enough questions about non-disclosure that the APS ordering rate will increase. More often than not, patients fail to remember the medications they use, or even the reason why they were prescribed. This is often independent of any desire for misrepresentation.

Having considered all of these issues regarding PDBs, it is just as important to consider the variety of uses of this tool. Certainly, it possesses value in the underwriting of both life and health products, even though the same drugs may have different implications for each of these categories. Some drugs might, for example, be highly associated with morbidity risk from disabling conditions, while at the same time having very little mortality risk.

Although PDBs should be beneficial for the full range of life products, possibly the largest value may be in simplified issue products that currently do not gather or verify a great deal of medical information. The addition of a prescription check would substantially increase the confidence that an underwriter is aware of significant health concerns without incurring substantial cost or time delays. At present, a PDB screen costs in the range of $15 and takes less than a minute to run. This tool appears to be a natural extension of automated risk assessment programs that quickly evaluate an applicant's suitability for insurability.

In addition to various underwriting applications, both for individual case assessments, as well as for pricing estimation, this tool should be highly useful in the area of claims analysis. The ability to see a decedent's prescription drug use prior to both application and time of death should provide valuable insights into misrepresentation issues, as well as provide direction on the need for medical history tracking.

Another potential use for PDBs is in the establishment for preferred class criteria. Appropriate routine screens for

prescription drug history may help establish a mortality class with better than average mortality. This potential for improved mortality has been demonstrated by our actuarial mortality analysis. However, its application as preferred class criteria requires considerable study with the need to evaluate the specifics of the use of the tool by age band, product line, terms of use and so forth.

In conclusion, PDB checks have the potential to substantially increase our knowledge of an applicant's health history and confidence that we have full disclosure of all known health conditions. When used appropriately, PDBs should increase our ability to accurately risk stratify and place each applicant into the appropriate risk pool. This should be valuable both in the substandard and preferred risk pools. Further experience and adaptation will help us understand how best to use this new and exciting tool in the same manner that we learned how to use prior tools such as blood testing. ■

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