COMMENTARY

Searching for Simplicity in the Complexity of Symptom Clusters

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Occam's razor proposes that the simplest solution is preferable; however, in the science of cancer and cancer symptoms, simple solutions have been elusive. Understanding individual symptoms continues to confound the science community, and symptom cluster science appears to be an incredibly complex schema of individual symptoms co-occurring and interacting with one another. The simplest explanation for symptom clusters would be a common underlying mechanism at the human genome level. Such a finding could greatly simplify and perhaps revolutionize symptom management.

Occam's razor is a philosophical and scientific principle suggesting that "entities are not to be multiplied beyond necessity" (Duignan, 2017, para. 1) and implying that the simplest solution is preferable. However, simple solutions have been rare in cancer science. The search for symptom science knowledge seems to be a series of ebbs and flows, careening from simple to complex and back to simple again. At each juncture of knowledge development, we suggest that applying Occam's razor to the direction of future research may simply be the best option.

The historic development of cancer knowledge has been eloquently outlined by Mukherjee (2010), who illustrated this ebb and flow. Cancer was initially understood as an abnormal growth cured by simple removal, but because widening surgical margins did not eradicate the disease, cancer became known as a complex array of diseases of different organs. Today, knowledge in genetics, molecular biology, and technology has re-conceptualized cancer more simply as a series of mutations to critical genes that result in the loss of control of three cellular functions: division, maturation, and death. These three functions initially appeared simple, but science has revealed increasing complexity as researchers identified multiple biologic pathways and genetic mutations that act alone and interact within the dynamic epigenetic environment. Finally, the turn toward individualized treatment in this era of personalized medicine can be conceptualized as a return to a simple N-of-1 approach to cancer care (Blix, 2014; Starkweather et al., 2013).

In "Factors Associated With Poor Sleep in Older Women Diagnosed With Breast Cancer" in the current issue, Overcash, Noonan, Tan, and Patel (2018) draw attention to another evolving knowledge area: the science of cancer symptoms and, specifically, how symptoms cluster among older adults with breast cancer. Driven by their clinical work with older patients with cancer, the frequency of complaints they received about poor sleep, and that "60% of older women diagnosed with breast cancer report poor sleep quality" (p. 359), Overcash et al. (2018) sought to uncover predictors of sleep quality. In their logistic regression model, pain, depression, and fatigue were related to poor sleep, but the model did not reach statistical significance. Their findings align with the psychoneurologic symptom cluster (pain, fatigue, sleep disturbance, and depression), which may be the symptom cluster most frequently reported by cancer survivors (Kwekkeboom, 2016). However, because of the complexity of symptom clusters within the already complex field of gero-oncology, Overcash et al. (2018) concluded that "each symptom is distinct, can behave clinically different, and can require individual management plans" (p. 365), an approach entirely consistent with pre–symptom cluster and current symptom management.

Early nursing research on cancer symptoms was arguably simplistic. Incidence rates, severity, and trajectories of individual symptoms have been described and individually managed (Fu, LeMone, & McDaniel,

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2004). However, symptom studies have reported wide variation in symptom experiences, often attributed to type or site of cancer and cancer treatment(s) and multidimensional aspects of symptoms. More than a decade later, Overcash et al. (2018) concluded that interventions were targeted to each individual self-reported symptom. When nurses began to question the frequent co-occurrence of symptoms, the science of symptom clusters began.

Since the early 2000s, researchers across multiple disciplines have proposed theories and tested models of symptom clusters. Early theoretical work proposed multiple models (Brant, Beck, & Miaskowski, 2010; Parker, Kimble, Dunbar, & Clark, 2005) in which underlying biologic, psychosocial, and behavioral mechanisms explain the co-occurrence of symptoms. Researchers have conducted descriptive and correlational studies to examine the association, interaction, synergy, and temporal nature of symptom clusters and have evaluated the effectiveness of multiple psychoeducational, cognitive behavioral, and biobehavioral interventions to ameliorate cancer symptoms (Miaskowski et al., 2017; Sullivan, Leutwyler, Dunn, & Miaskowski, 2018). Knowledge of individual symptoms has expanded to include how symptoms interact with one another in the biobehavioral and psychosocial environment of the individual. However, after almost 20 years of concerted research efforts, no common definition, consistent measurement standards, or even a basic understanding exists of why and how symptoms cluster among individuals with cancer (Barsevick, 2016).

Kwekkeboom et al. (2018) suggested four potential origins of symptom clusters:

- Cancer and its treatment may cause multiple symptoms.
- One symptom may cause other symptoms.
- Treatment for one symptom may cause other symptoms.
- An underlying mechanism may cause the entire cluster.

Much research has focused on the fourth potential cause and underlying mechanisms, predominately the immune/inflammation pathway, but inconsistent findings require continued investigation (Lynch Kelly et al., 2016). A new psychoneuroimmunology model of symptom clusters (Starkweather et al., 2013) and new analytic strategies used in symptom cluster research have created complex schemas for understanding cancer symptom clusters. Still, all this work has yet to uncover a simple solution or, really, any solution for clinicians (Kwekkeboom, 2016). Perhaps it is time to look for a simpler option for understanding cancer symptom clusters.

We argue that before the science community can understand causal mechanisms for symptom clusters, it must understand the etiology of individual symptoms. This very basic, direct, and simple approach has not yet produced sufficient knowledge needed for symptom management solutions. Cancer-related fatigue, for example, although studied extensively, has no clear, substantiated etiology. Enter the human genome, which was mapped completely at about the same time as symptom cluster research began in earnest. The genetic/genomic revolution may finally give us the simple, razor-sharp solution to symptom management and symptom clusters. Genes code for every protein that directs cellular activity; could the common pathway to explain symptom clusters be a mutation in one or more gene(s) or an error in the epigenetic environment? Does the persistence of symptoms, many lasting years and even decades post-treatment, suggest a self-perpetuating genetic/genomic aberration? Of course, symptom scientists are investigating these hypotheses (Lopes-Júnior et al., 2016; Lyon et al., 2014; Miaskowski & Aouizerat, 2012). A common underlying mechanism for clustering symptoms at the very basic level of the human genome would provide a target for interventions that could greatly simplify and perhaps revolutionize symptom management and relieve patient symptom burden.

Overcash et al. (2018) were looking for practical, effective solutions to clinical problems, in this case, how to alleviate sleep disturbance in older women with breast cancer. It is not surprising that their study, although adding to current knowledge of the co-occurrence of symptoms, did not offer a simple solution to the sleep problems of older women with cancer. Science is not there yet. Their findings confirmed the need for continued research in this area. However, they did find that fatigue was the strongest predictor of poor sleep. Although temporal precedence in the fatigue–sleep correlation has not been established, symptom management for fatigue includes only one effective, evidence-based intervention: exercise. Overcash et al.'s (2018) proposition of using "exercise as medicine" (p. 367) following established guidelines for physical activity in older adults is a sensible, health-promoting, and evidence-based intervention. Symptom cluster science has gone from simple to exponentially complex, yet a simple underlying genetic explanation may be the answer.

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