

# Society for Investigative Dermatology Skin Disease Co-Morbidities Project Launch Conference Proceedings

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Approximately 90 dermatologic researchers from academia, government, and industry convened in October 2008 for the Burden of Skin Disease Co-Morbidities Project Launch Conference.\* The conference, sponsored by the Society for Investigative Dermatology (SID), was organized by Lowell Goldsmith, Senior Scientific and Medical Advisor; Becky Minnillo, Senior Director, Programs and Research; and Dennis Barbour, Chief Executive Officer. The overarching goal of this conference, which launches a multi-year, multidisciplinary project, was to facilitate interaction and collaboration across multiple clinical and basic science disciplines, including dermatology, cardiology, oncology, psychiatry, epidemiology, and industry. Through research presentations, examination of the existing data resources, and group panel discussions, the participants were able to identify potentially productive interdisciplinary collaborations and funding sources. SID plans to partner in this effort with government, industry, academia, and the nonprofit and for-profit health sectors.

For the purposes of this initiative, comorbidity refers to the presence of skin disease concurrent with one or more conditions that occur with prevalence higher than chance. In this respect, dermatological disease may be the cause, an associated risk factor, or a predictor of comorbidity. The simultaneous presence of skin disease and a second condition makes the study of these conditions complex and emphasizes the need for collabora-

tion among experts from several disciplines. Associations between skin disease and cardiovascular disease, skin disease and psychiatric disease, and adverse skin reactions and toxicity of drug therapies, mostly oncology drugs, were examined in detail during the conference.

In the keynote address, Brian Strom, from the University of Pennsylvania, described epidemiological approaches to studying drug-induced disease. The emergence of new classes of therapeutic agents for skin diseases and reactions of new drugs that involve the skin made this a cogent keynote subject. Pharmacoepidemiology involves the study of the use and effects of a drug in a population. It is particularly important for dermatology because skin reactions are the most common adverse drug reactions (ADRs). Premarketing drug safety studies yield incomplete information about adverse events. Postmarketing studies, on the other hand, are potentially more powerful; however, submission of data for these studies has not always been required. In fact, these studies commonly arise out of crises observed during patient use in large and often unintended populations. Uniquely, pharmacoepidemiology studies are influenced by the major role that industry plays as well as the interplay among industry and government regulators and the enormous public interest in drug safety. Results from these studies can delineate risk factors for drug-induced disease, describe pharmacogenetics, suggest mechanisms for molecular pharmacoepidemiology, and describe

drug interactions. In sum, the analysis of pharmacoepidemiologic data is critical for understanding the effects of drug therapy on patients in the face of the inherent problems of the drug approval process; however, the lack of trained personnel and the difficulty in obtaining adequate data pose challenges to be addressed in the future.

Mark Udey, from the National Institutes of Health, talked about the systemic signs of skin disease. Although it is clear that skin signs frequently reflect systemic disease, it is also reasonable to expect that systemic signs reflect skin disease. Indeed, identification of comorbidities can lead to improved patient health via early intervention or prevention strategies as well as to insight into the pathogenesis of morbid conditions. As a result, the study of comorbidities by dermatologists is critical. A laundry list of challenges, however, must be overcome. To study a comorbidity, the important questions must be well defined in order to elicit the necessary data in a way that changes medical practices for improved health. Interestingly, the relevance of these findings may extend beyond the condition being studied. In addition, the necessary resources for these studies must be developed, including data sources, partnerships, and funding sources. Perhaps most importantly, enhanced interaction between dermatologists and other specialists in the health-care community will undoubtedly benefit the study of comorbidities and allow dermatologists to make a greater impact on patient health in general.

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### Dermatotoxicity

One of the key areas of interest for the study of comorbidity of skin diseases is the effect of drugs on the skin. Mario Lacouture, from Northwestern University, discussed dermatotoxicity, including the direct effects of drugs on rapidly proliferating cells, adverse reactions, and extravasation reactions. Dermatotoxicity is a particularly compelling field of research because some 500,000 people will undergo chemotherapy and 800,000 will undergo radiotherapy this year, and the most commonly used oncology drugs give rise to frequent dermatologic toxicities compared with other marketed drugs. Indeed, the success of the new-generation targeted anticancer therapies is often predicted on the basis of the accompanying skin toxicity. Dermatotoxicities often seriously impact patients' quality of life and may lead to curtailment of treatment. Only about 8% of oncologists refer patients to dermatologists for these issues, although dermatotoxicities cause 32% of patients to discontinue therapy and an additional 60–76% of patients to reduce or interrupt therapy. Dermatotoxicities are amenable to study and therapy development, and at least 24 trials are under way in an interdisciplinary setting to address these clinical needs.

Edward Cowen, from the National Cancer Institute, described a specific system for examining dermatotoxicity in the context of comorbidity. Graft-versus-host disease occurs in a significant number of allogeneic stem cell transplantation patients, and in 75–90% of these people, the skin is affected. Comorbidities include permanent disfigurement, pain, pruritus, wound infection, functional limitations, and therapy-associated side effects such as infection. Corticosteroids are the most effective therapy for GVHD, but these bring relief to only about 25% of patients. This disease is quite difficult to study because of its rarity; thus, institutional or even multi-institutional, multidisciplinary collaboration is needed. A diagnostic instrument for severity and a multi-organ approach, complete with appropriate specialist referrals, is

required to gain a better understanding of the disease pathogenesis and to develop appropriate therapies.

In the dermatotoxicity breakout session, Charles Bennett, from Northwestern University, described the Research on Adverse Drug Events and Reports project. This postmarketing pharmacovigilance initiative aims to detect ADR signals, investigate ADR occurrences, analyze these data, and disseminate the results. This project is important for dermatologists because the larger, more comprehensive data sets include reports of adverse effects by all clinicians, and they may indicate skin effects as merely a "rash" without a clinical diagnosis. Other registries and data sets that are available for this type of analysis include the United Kingdom's General Practice Research Database, the Food and Drug Administration (FDA) Adverse Events Reporting System (AERS), and MedWatch reports, although these data are ill suited for dermatologic analysis. Recently, a significant number of large pharmaceutical companies have combined data on skin reactions to facilitate data mining for dermatotoxicity. It is difficult to determine whether the drug was in fact the cause of the adverse reaction in these patients. Additional studies will be necessary to examine this issue in detail. Furthermore, studies of dermatotoxicity with genetic and immune susceptibility factors may be of use in the identification of patients at greater risk for adverse events. Finally, increased data availability, more complete reaction accounts, and standardized reporting forms would benefit dermatotoxicity research.

### Dermatologic–psychiatric disease

Francisco Tausk, from the University of Rochester, led a discussion about comorbidities in psychiatry and dermatology. Psychiatric disease influences the development of skin diseases through the effects of stress, depression, and anxiety. Not surprisingly, treating psychiatric comorbidity improves skin disease, and vice versa. For example, etanercept has been shown to improve depression and psoriasis concurrently. Despite these observations and the high

prevalence of psychiatric and dermatologic comorbidities, a lack of common instruments for measurement, inadequate numbers of trained individuals, difficulty in obtaining funding, insufficient epidemiological data, and a lack of integrated treatment facilities prevent these conditions from being treated or researched effectively and in concert. In Europe, however, psychodermatology meetings have been well attended, educational programs for management of skin diseases have been implemented, and a certification program has been established. North American efforts in psychodermatology may be initiated using the European model.

In the breakout session on dermatologic–psychiatric disease, contributors contrasted the available tools and data sources with the need for extensive strides in this arena. Alexa Kimball, from Harvard University, described the importance of quality-of-life assessment. The analysis of quality of life with respect to skin disease overlaps with psychiatric findings in such areas as anxiety, frustration, embarrassment, annoyance, and depression, and a substantial burden on patients with skin disease has been observed. Whereas comorbid mental illness is typically diagnosed by a physician, quality-of-life issues (particularly appearance) are most often reported by the patient. Good therapy improves quality of life, but it is not yet known whether such therapy improves comorbid mental illness. Researchers need to understand the interactions between quality of life and comorbid mental illness, develop tools for diagnosing psychiatric illness and assessing improvement in trials, and determine how psychiatric illness is coded in databases to allow researchers access to archived data for dermatologic–psychiatric studies. According to Phillip Harvey, from Emory University, neuropsychiatric conditions account for 9 of the 10 most common causes of disability, whereas skin conditions are not reported to be a significant cause of disability. The reporting of psychiatric symptoms, by patients or by physicians using standardized scales, may be biased according to clinician expertise and patient perception and literacy. The

determinants of real-world disability are a challenge to assess. Interestingly, the causal models for dermatological conditions suggest different points for intervention. For example, does itching lead to depression, which leads to disability, which leads to lower quality of life? Or does itching lead to disability, depression, and reduced quality of life, which are all merely correlated? Peter Muehrer, head of the comorbidity program at the National Institute of Mental Health, indicated that no studies of mental disorders in patients with skin disease are currently funded through the institute. With this he confirmed not only the need for this type of research but also the potential availability of funding for these studies.

#### **Cutaneous–cardiovascular disease**

Expanding on the association between skin disease and systemic disease, Joel Gelfand, from the University of Pennsylvania, discussed the apparent link between psoriasis and cardiovascular disease (CVD). Psoriasis, which affects more than 70 million people, is an inflammatory disease with complex etiology, and inflammation is known to contribute to chronic diseases such as atherosclerosis, diabetes, and obesity. The risk of mortality in patients with psoriasis is 50% greater than in healthy individuals, perhaps because of the central role of inflammation in the pathogenesis of atherosclerosis and myocardial infarction. Psoriasis is also associated with additional CVD risk factors, including smoking, obesity, dyslipidemia, hypertension, and diabetes. Severe psoriasis is associated with increased risk of myocardial infarction and coronary artery disease. These associations suggest countless areas for investigation.

In the breakout session on cutaneous–cardiovascular disease, contributors reexamined the link between psoriasis and CVD and discussed data needs and potential sources. Both Kevin Cooper, from the University Hospital at Case Western Reserve University, and Eric Yang, from the University of North Carolina, discussed the role of inflammation in psoriasis and CVD. Investigation into whether aggressive treatment for psoriasis inflammation

reduces atherosclerosis and the frequency of myocardial infarction and whether aggressive atherosclerosis treatment reduces psoriasis symptoms is warranted but requires specialized expertise, high-quality data, broad and unbiased participation, and the participation of community-practice physicians. The Case Western collaboration between a newly funded Center of Research Translation for psoriasis and the Murdough Family Psoriasis Center is one example of an approach to this field of investigation.

Joel Kremer, from the Albany Medical College Center for Rheumatology, presented information about the industry-sponsored Consortium of Rheumatology Researchers of North America (CORRONA) database, which includes 31,000 patient years of follow-up of rheumatoid arthritis, psoriatic arthritis, and osteoarthritis patients. The goal of this large, long-term database is to provide information on the safety and efficacy of agents used in the treatment of these diseases. Registries such as CORRONA and the British Society for Rheumatology Biologics Registry are a significant challenge in the United States, which lacks a centralized medical record system and is plagued by issues related to the Health Insurance Portability and Accountability Act, selection bias, lack of representation of the general population, and under-represented academic institutions. The CORRONA database, however, includes thousands of individuals with psoriatic arthritis and, despite its inherent limitations, is an excellent source of data for studying the associations among inflammation, psoriasis, and CVD.

The following questions are at the top of the anticipated research agenda: What is the risk of CVD? How do other factors affect this risk? Does aggressive treatment of psoriasis reduce CVD risk? Does aggressive treatment of atherosclerosis reduce psoriasis symptoms? What are the mechanisms of these interactions?

#### **Resources for research**

Several presenters from academia, government, and industry described

the advantages and limitations of the databases and related resources for investigating skin disease comorbidities. According to Robert Lew, from the Veterans Administration (VA), the VA has resources for dermatologic research, including VA study design and database resources, the Epidemiology Research Information Center, a clinical trial coordinating center, and the VA core laboratory for blood and tissue sample storage. These resources include 12 million electronic records with an average of 5 years of follow-up. Outside investigators must collaborate with experts within the VA, the population served is very selective, and the records are difficult to abstract. However, this massive resource is worth exploring, and it even offers internal support in medicine, information technology, epidemiology, and statistics.

The FDA also offers extensive data resources for clinical research. The clinical safety database is the result of premarketing drug safety studies, but other, more robust postmarketing safety information is also archived. Both MedWatch reporting and the Adverse Events Reporting System reports are available for downloading. These sources are especially useful for detecting the signal of unsafe reactions, although the data cannot be used for prevalence or causality assessments based on the lack of perfect reporting by patients and physicians. Furthermore, the National Cancer Institute sponsors the Surveillance Epidemiology and End Results Program, which, since 1973, has provided information on incidence, survival, and prevalence from specific geographic areas representing 26% of the US population. The US Centers for Disease Control and Prevention also offers online databases and surveillance systems that can be tapped by outside researchers.

Private sources of data, although more difficult to access, are also available. Maryam Asgari, from Kaiser Permanente, described the Kaiser Research Database, which includes electronic data records from 1968 onward for 8.5 million patients seen by almost 13,000 physicians. This

large data set includes patient demographics, diagnoses, procedures, labs, pharmacy data, inpatient admissions, electronic pathology, and additional details such as occupation, family history, and body mass index. These data, in particular, lend themselves to research on dermatotoxicity because of the electronic pharmacy and diagnoses records. Research is being carried out on dermatology comorbidities within Kaiser; however, additional studies with collaborating outside investigators are limited by the this HMO's small research staff.

In addition to these broader generalized databases, pharmaceutical companies and academic researchers have developed their own targeted data sets. For example, Stephen Rozzo, from Abbott, described the HUMIRA registry, which includes data on 6,000 psoriasis patients. This postmarketing multinational commitment is focused on archiving adverse events to evaluate the long-term safety and effectiveness of adalimumab. This registry offers data regarding safety, work productivity, activity impairment, dermatologic life quality index, and patient global assessment. Marc Chevrier, from Centocor, described the current use of biologic cohort studies to address the difficulties in dermatology registries, such as primary care of patients at sites other than the site of the dermatologist, finding rare events requiring a large number of patients, and the typical simplified data set structure used for consolidation of data from multiple sources. Thus, multicenter biologic observational cohort studies can be performed to examine therapies in the actual clinical setting, incorporate comparator cohorts, and optimize the ability for in-depth analysis of particular contexts. Effectiveness, safety, product, and disease registries are options for addressing specific data needs. At the University of Texas MD Anderson

Cancer Center, Madeline Duvic is spearheading one such endeavor, the National Alopecia Areata Registry, to investigate familial genetic associations and quality-of-life issues. It involves participation in a Web-based, patient-friendly registry at five institutions, followed by a physical exam to confirm alopecia areata. Sera and DNA samples are taken for analysis. This registry of 6,500 patients has enabled confirmation of association with HLA alleles, studies of cytokine profiles, and a case-control study on autoimmunity.

### Conclusions

Comorbidity as a concept is clearly not well defined, and the term can be used for causes, effects, and confounders. The current research agenda aims to gain a mechanistic understanding of drug reactions and their relationship to host susceptibility factors, a mechanistic understanding of the effect of skin diseases on the psyche and of the psyche on skin diseases, and a mechanistic understanding of the effect of inflammatory skin diseases on various organ systems such as the cardiovascular system, the central nervous system, and the liver. Investigation into these broad areas will require extensive collaboration among individual researchers in multiple disciplines, and these collaborations must include a host of institutions to ensure success.

Training in statistics and pharmacoepidemiology for junior faculty and residents is especially important. The American Skin Association offers individual fellowships in epidemiology for dermatology residents, and entry level grants are available; however, funding for senior level work in these fields has historically been difficult to obtain. Increased funding for individual investigators and collaborative efforts in these areas would advance this line of investigation.

In a final analysis of the meeting, Lowell Goldsmith, from the University of North Carolina, and Brian Strom summarized the next logical steps to enable investigation of comorbidities and to facilitate interdisciplinary collaborations. Importantly, the questions should be focused and well defined, and the necessary data should then be collected and/or databases queried. Many registries and databases are available, although each has its limitations and inherent biases that must be acknowledged. The importance of multidisciplinary teams of both clinicians and methodologists is unmistakable. Each brings unique expertise and perspective, essential for asking the right questions and formulating the correct methodologies.

To promote the investigation of comorbidities of skin disease, the SID will disseminate the information discussed at this conference through specialty journals and other media sources as well as Web-based slide presentations and webinars. Online resources will include a database of comorbidities publications; development of communications forums for meeting attendees, junior faculty, and residents; links to participants' names, affiliations, and research interests; and information about laboratories that wish to be involved in this cutting-edge research. In addition, a separate Co-Morbidities Symposium will be held at the 2009 Annual SID Meeting in Montreal. Overall, the success of this SID project will depend on how effective this group can be in facilitating the creation of research teams that span a variety of disciplines.

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*\*The Burden of Skin Disease Co-Morbidities Project Launch Conference was held at the Bethesda North Marriott Hotel and Conference Center, Bethesda, Maryland, on 15-16 October 2008. The conference was sponsored by the Society for Investigative Dermatology.*