



We can learn a lot from drug adverse effects

No one likes adverse effects from medications. Some seem to occur as random events; others are predictable based on known pharmacologic properties of a drug or its metabolites, or are monitored for after published reports of anecdotes. Adverse effects can also teach us important things about human biology.

Some drugs exhibit a dose-toxicity relationship that is sufficiently predictable to permit drug-level monitoring to limit renal or other toxicity. Others cause ocular or marrow toxicity that can be limited by weight-based dosing and careful monitoring. With azathioprine, some toxicity can be predicted by assessing the activity of the enzyme thiopurine methyltransferase, which metabolizes the drug. Other approaches to using pharmacogenomics have included HLA-B locus haplotyping to detect increased risk of immune-mediated toxicities of drugs such as carbamazepine and allopurinol. Both of these drugs exhibit serious systemic toxicities that are incompletely understood, but these are nascent and significant steps toward providing personalized (precision) medical care.

Adverse effects of some drugs may result from their intracellular effects, which are only partially predictable by drug levels or dosing. Colchicine, hydroxychloroquine, and amiodarone all affect intracellular vacuolar transport and lysosomal processing. Yet, although the footprints of drug effect can be seen in many histopathology samples, only some patients—but maybe more than currently recognized—suffer cardiac and skeletal muscle vacuolar myopathy, axonal neuropathies, or pulmonary or retinal cell toxicity from these drugs. But distinguishing the histopathologic footprints of drug exposure and the biologic effect from true drug toxicity with organ damage is not always straightforward.

Rare adverse effects may only become apparent with frequent use of a drug in the general community. These often remain mechanistically unexplained: Why can minoxidil cause pericardial effusions or a nonsteroidal anti-inflammatory drug cause aseptic meningitis? Some effects may be due to altering of the unique balance of biochemical pathways in a given patient, leading to unexpected drug metabolism with generation of toxic metabolites.

More interesting to me are effects that are seemingly off-target biologic outcomes caused by disrupting normal physiologic homeostasis and stimulating counterregulatory pathways in such a way that unexpected biologic effects occur. Angioedema and cough in some patients who have taken angiotensin-converting enzyme inhibitors are examples, but why the disturbed control mechanisms lead to these effects in only occasional patients is still incompletely elucidated.

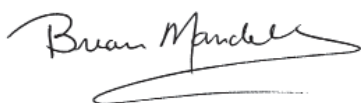
Two additional classes of drugs with unique systemic adverse effects are discussed in this issue of the *Journal*. The “flulike” syndrome after bisphosphonate treatment, presumably resulting from selective cytokine release by macrophages that have ingested certain bisphosphonates, is a not uncommon and significant annoyance to many patients, and in my experience it is a reason patients discontinue the treatment. Lim and

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Bolster (page 675) describe the reaction and their approach to its management, and comment on the fairly obscure pathway that may explain its occurrence. Again, it is not clear to me why only relatively few patients experience the reaction. Is there a genetic predisposition? Or is it influenced by the patient's baseline "inflammatory tone," as influenced by the state of his or her microbiome or other still uncharacterized factors? And why does this reaction often diminish with repeated dosing of the drug?

Most striking is the description and discussion by Khan et al (page 679) of the management of autoimmune colitis after administration of immune checkpoint inhibitor anticancer therapies. These drugs represent important advances in the therapy of various cancers. They are novel in that they are not specific to tumor type, although certain drugs within this new class of immunotherapy seem to exhibit more dramatic and enduring responses against one type of cancer than against another. These therapies are not directly tumor-reactive, but act by down-regulating the normal "brakes" or checkpoints of the immune system that normally play a role in reigning in the immune-inflammatory system response to infection once the offending infective agent is neutralized. These checkpoints have also been thought to limit the development of autoimmunity. Many cancers seem to capitalize on the activation of these brakes to evade tumor immunity. That these checkpoint therapies are so effective in some patients with heretofore unresponsive cancers is obviously a major advance. But equally striking is the scientific proof of the immunologic concept that by inhibiting these normal brakes on inflammation there is loss of normal regulation of the immune response and autoimmunity ensues unchecked. Khan et al discuss the colitis that can occur with these therapies, but a host of fascinating and potentially life-threatening organ-specific complications can be invoked by the checkpoint inhibitors, including hypophysitis, myositis, nephritis, and pneumonitis. What determines which patient will suffer these immune complications, which organs will be affected in a given patient, and the relationships between preexisting autoimmune disease, antitumor response, and these autoimmune complications are still being unraveled.

If you have not yet encountered patients with these complications in your practice, it is quite likely you will. The topic is worth reading about now (see the review by June et al¹), and we will provide additional reviews in the future.



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1. June CH, Warshauer JT, Bluestone JA. Is autoimmunity the Achilles' heel of cancer immunotherapy? *Nat Med* 2017; 23(5):540–547. doi:10.1038/nm.4321. Correction in *Nat Med* 2017; 23(8):1004. doi:10.1038/nm0817-17-1004b.