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EDITORIAL

SILVER BULLETS AND SHOTGUNS IN LYMPHEDEMA THERAPY

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A recent *Wall Street Journal* feature article (1) raised the question of whether the United States Food and Drug Administration (FDA)'s carefully controlled evidence-based focus on approving only effective single drug therapeutic agents ("silver bullets") is the wisest and most practical way to develop new and improved treatments for a variety of diseases. The author argues that the "oriental" approach of combination therapies ("shotguns"), e.g., herbal recipes often supplemented by manual/manipulative maneuvers is cheaper and may be as efficacious even if convincing evidence is not provided for each component's activity. As these alternative/integrative therapies and spa destinations that offer them have become increasingly popular around the world, the shotgun approach using botanicals has finally found its way into new FDA guidelines, and both approval processes now work in parallel (albeit unequal) tracks.

Lymphedema research, as reflected in the pages of *Lymphology* including the current issue, is a microcosm of this global debate–global in the sense that the dialog reflects the world's different cultures and practice environments and global in that lymphedema therapeutic regimens have traditionally been multimodal rather than isolated monotherapies.

In this issue, Narahari et al (2) describe a detailed community-based complex multimodal treatment regimen including components of combined physiotherapy (CPT), Aruyvedic medicine, and culturally sensitive manipulations. The authors argue that each treatment component is cheap, easily provided after brief training, culturally sensitive, and capable of widespread compliance. This "multi-barreled shotgun" approach may not satisfy the purist proponents of "silver bullets," but as the authors suggest, the design, methods, and conclusions should fit the study environment (whether academic medical center or remote village). In the final analysis, successful replicable results with a wide margin of safety should be the primary goal. Is it really worth dissecting out the active components (if even possible since some may involve synergistic interactions) to find the single "silver bullet" if an inexpensive, low-risk "shotgun" works?

Furthermore, CPT, the ISL-consensus-recommended current optimal treatment for peripheral lymphedema, is admittedly multi-modal even though unbundled individual components of CPT (MLD or multilayered compression bandaging) may be efficacious "silver bullets" when targeted to well-defined groups of patients. Compression pumps and massaging devices are seldom used alone for treatment but rather supplemented with active and maintenance compression. Many patients with lymphedema also add an array of over-the-counter remedies and physical maneuvers on their own. Various surgical procedures–liposuction, lymphatic-venous or

lymphnode-venous shunt operations, and lymphatic transplantation–in carefully selected patients may be "silver bullets" but they are generally combined with some form of long-term compression and often preceded by maximal CPT decompression pre-operatively. And it is hard to dodge the cosmetic and physically enabling "silver bullet" of appropriately timed debulking operations for reducing the deformities of elephantine genitalia and limbs. But even these incorporate MLD and/or compression for augmentation and maintenance of the operative results.

Envisioning futuristic "magic bullets," one wonders how will new molecular-targeted drugs, cell-based therapies, and tissue engineering approaches for lymphedema be tested for efficacy? Will each stand alone or need boosting or modulation by various physical maneuvers or pharmacologic agents (thereby becoming "clusters" of silver bullets or elegant shotguns)? And will unforeseen risks arise when these finely honed "molecular bullets" hit their targets but perturb other vital processes or promote pathologic ones (e.g., growth factor therapy for cancer treatment-related lymphedema or stem cells gone awry) and then require even more complicated therapeutic armor to protect patients against the unintended damage.

What should be asked of clinical trials in lymphedema research? At a minimum, they should be: ethically conducted (informed consent and free from financial conflicts of interest); appropriately designed for the study populations, closely monitored, analyzed objectively, and capable of replication with a low risk to benefit ratio. Although a less belligerent war metaphor might be more appropriate, we welcome continuing dialog on the "silver bullets vs. shotgun" issue and its application in lymphology.

REFERENCES

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