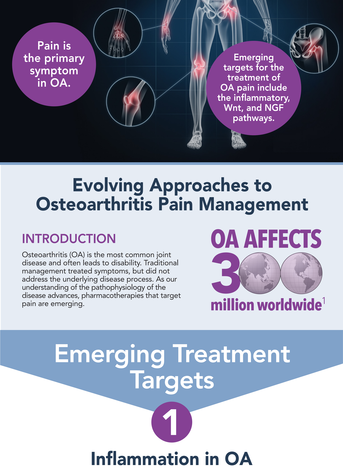
OSTEOARTHRITIS MEDICATIONS

Targets of New Treatment Options

OVERVIEW



OA is a complex heterogeneous disease that affects all structures of the joint.

Pain is the primary symptom in OA.

Emerging targets for the treatment of OA pain include the inflammatory, Wnt, and NGF pathways.

Evolving Approaches to Osteoarthritis Pain Management

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease and often leads to disability. Traditional management treated symptoms, but did not address the underlying disease process. As our understanding of the pathophysiology of the disease advances, pharmacotherapies that target pain are emerging.

OA AFFECTS 3 million worldwide[1]

Emerging Treatment Targets

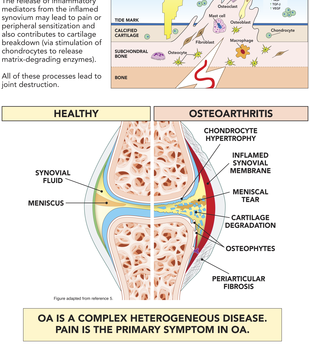
1 Inflammation in OA

It appears that the inflammatory process of OA is a result of a combination of pathological processes.

OA develops as a result of changes in the synovial joint. Microfractures in the bone-cartilage interface allow entry from subchondral bone of cellular elements contributing to the OA process.

The release of inflammatory mediators from the inflamed synovium may lead to pain or peripheral sensitization and also contributes to cartilage breakdown (via stimulation of chondrocytes to release matrix-degrading enzymes).

All of these processes lead to joint destruction.



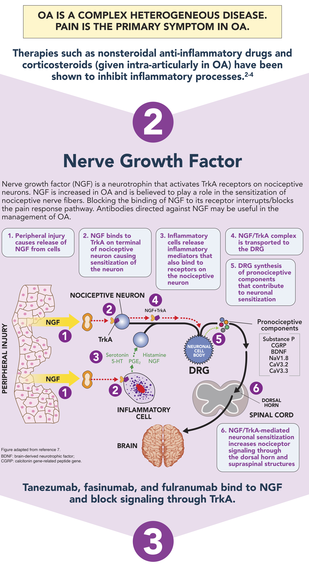


Figure adapted from reference 5.

OA IS A COMPLEX HETEROGENEOUS DISEASE. PAIN IS THE PRIMARY SYMPTOM IN OA.

Therapies such as nonsteroidal anti-inflammatory drugs and corticosteroids (given intra-articularly in OA) have been shown to inhibit inflammatory processes.[2-4]

2 Nerve Growth Factor

Nerve growth factor (NGF) is a neurotrophin that activates TrkA receptors on nociceptive neurons. NGF is increased in OA and is believed to play a role in the sensitization of nociceptive nerve fibers. Blocking the binding of NGF to its receptor interrupts/blocks the pain response pathway. Antibodies directed against NGF may be useful in the management of OA.

1. Peripheral injury causes release of NGF from cells
2. NGF binds to TrkA on terminal of nociceptive neuron causing sensitization of the neuron
3. Inflammatory cells release inflammatory mediators that also bind to receptors on the nociceptive neuron
4. NGF/TrkA complex is transported to the DRG
5. DRG synthesis of pronociceptive components that contribute to neuronal sensitization

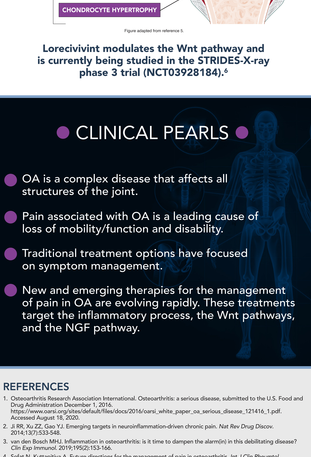


Figure adapted from reference 7.
BDNF: brain-derived neurotrophic factor; CGRP: calcitonin gene-related peptide gene.

6. NGF/TrkA-mediated neuronal sensitization increases nociceptor signaling through the dorsal horn and supraspinal structures

Tanezumab, fasinumab, and fulranumab bind to NGF and block signaling through TrkA.

3 The Wnt Pathway

Wnts are signaling glycoproteins that control cell proliferation, differentiation, apoptosis, migration of cell types, and cell survival.

Wnt signaling molecules and regulators are abnormally activated and/or suppressed in OA. Modulation of Wnts may be important treatment pathways for OA.

Figure adapted from reference 5.

Lorecivivint modulates the Wnt pathway and is currently being studied in the STRIDES-X-ray phase 3 trial (NCT03928184).[6]

CLINICAL PEARLS

- OA is a complex disease that affects all structures of the joint.
- Pain associated with OA is a leading cause of loss of mobility/function and disability.
- Traditional treatment options have focused on symptom management.
- New and emerging therapies for the management of pain in OA are evolving rapidly. These treatments target the inflammatory process, the Wnt pathways, and the NGF pathway.

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