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Pharmacological advances for treatment in Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) is a lethal, X-linked muscle-wasting disease caused by lack of dystrophin, essential for muscle fibre integrity. Despite extensive pre-clinical studies, development of an effective treatment has proved challenging. More recently, significant progress has been made with the first drug approval using a genetic approach and the application of pharmacological agents which slow the progression of the disease. Drug development for DMD has mainly used two strategies: (1) the restoration of dystrophin expression or the expression of the compensatory utrophin protein as an efficient surrogate, and (2) the mitigation of secondary downstream pathological mechanisms. This review details current most promising pharmacological approaches and clinical trials aiming to tackle the pathogenesis of this multifaceted disorder.

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Introduction

Duchenne muscular dystrophy is an X-linked recessive progressive wasting disorder caused by loss of function mutations in the dystrophin gene [1••]. DMD affects 1 in 5000 male births [2••] and is generally diagnosed between 2 and 5 years of age as motor developmental delay and abnormal gait, weakened proximal muscles and calf muscle pseudohypertrophy become apparent. Progressive muscle degeneration leads to loss of ambulation at 8–12 years with premature death at 20–30 years due to respiratory and cardiac complications [3].

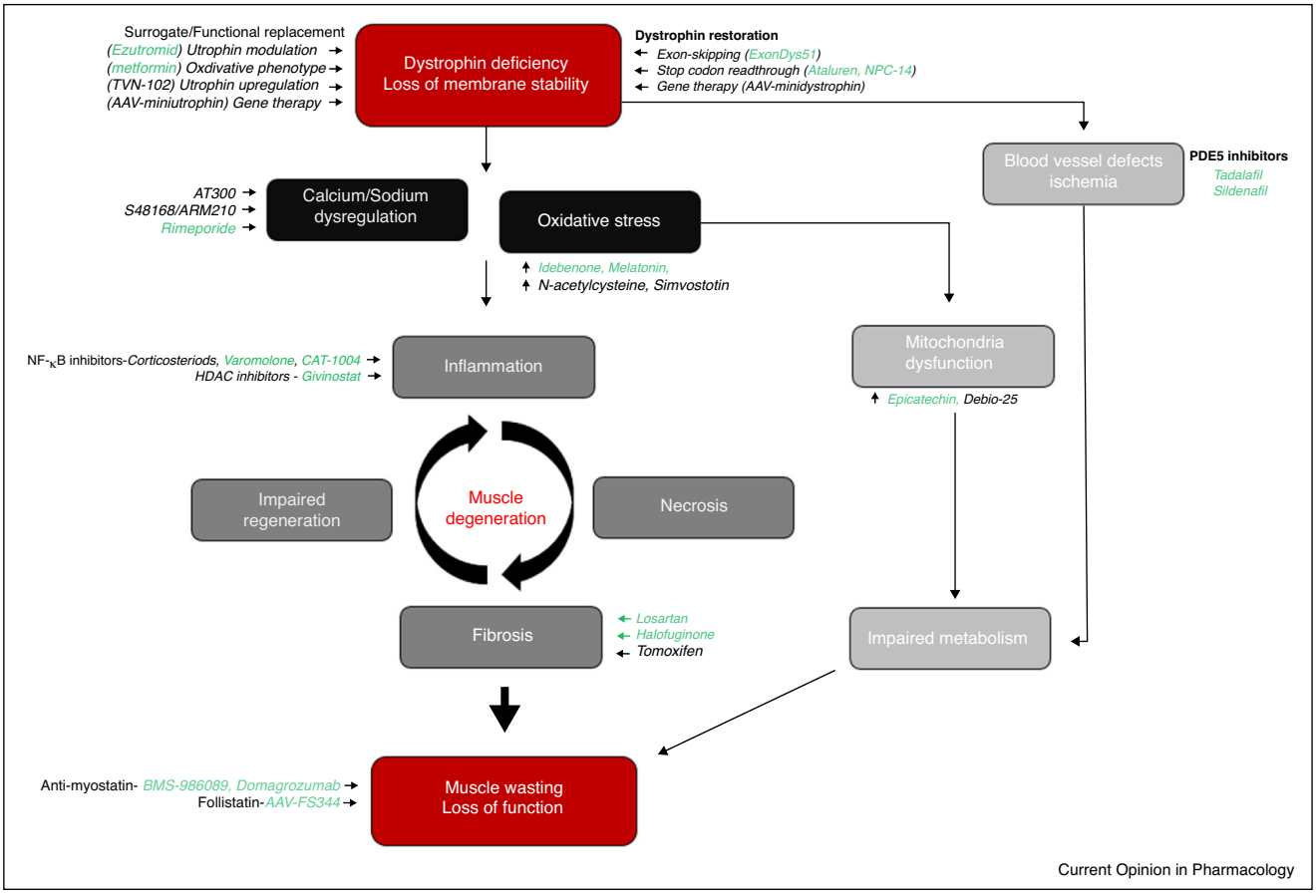
The DMD gene, consisting of 79 exons, spanning 2.3 Mb of genomic DNA, is the largest known gene in humans [4] and shows one of the highest spontaneous mutation rates. About 68% of the mutations are 'out of frame' deletions disrupting the translational reading frame resulting in loss of dystrophin. 'In-frame' mutations result in truncated but semi-functional dystrophin proteins which lead to Becker muscular dystrophy (BMD, MIM #300376), a clinically milder disease [5]. Duplications represent 11% and small mutations 20% of DMD cases respectively [2••].

Dystrophin is a 427 kDa cytoplasmic protein, which is a vital component of the dystrophin-associated protein complex (DAPC) at the sarcolemma, connecting the internal cytoskeleton to the surrounding extracellular matrix. Dystrophin provides structural stability to the skeletal muscle, maintains strength and flexibility and protects the sarcolemma from contraction-induced injury [1••]. Absence of dystrophin and subsequent loss of the DAPC leads to progressive defects including perturbation of the calcium homeostasis, activation of proteases and pro-inflammatory cytokines, and mitochondrial dysfunction resulting in continual influx of inflammation, fibrosis, repeated cycles of necrosis and altered regeneration, with impaired vascular adaptation (Figure 1). The myofibres become more susceptible to contraction-induced injury, which results in premature death, muscle wasting and fatty tissue replacement [6].

Despite exhaustive clinical management and corticosteroid treatment, there is currently no effective treatment for DMD, although considerable progress has been made recently in genetic approaches [7,8]. However, only one exon skipping drug, Exondys51 (Sarepta Therapeutics), has been given conditional approval by the U.S. Food and Drug Administration (FDA) [9]. Translarna (PTC Therapeutics) for reading through of stop codons has received conditional approval from the European Medicines Agency (EMA) but not FDA. These drugs are mutation specific and effects on heart muscle have not been reported. Thus, a therapy which targets all limb, respiratory and cardiac muscles and applicable to all DMD patients is urgently needed.

Current pharmacological intervention for DMD can be categorized into two groups: (1) strategies targeting the primary defect and (2) approaches to mitigate secondary and downstream pathological mechanisms. In this review, we summarize the recent most promising pharmacological therapies for DMD that have been tested in clinical trials or are efficient in preclinical models.

Figure 1



Pathophysiological consequences of the dystrophin deficiency and current therapeutic intervention investigated.
Loss of dystrophin and consequential loss of the DAPC enhances sarcolemma susceptibility to contraction-induced damage. Sarcolemmal lesions and possibly leaky Ca^{2+} channels increase calcium influx into dystrophic fibres. This leads to protease activation and free radical formation via cytosolic and mitochondrial sources triggering muscle degeneration with chronic inflammation. In parallel, defects in blood vessels trigger an ischemia and mitochondrial dysfunction which results in impaired ATP production and metabolic function. Drugs in green are currently being tested in clinical trials.

Pharmacological approaches that target the primary defect and aim to reconstruct the DAPC

Read-through of premature termination codons

Nonsense mutations generating stop codons leading to premature translational termination occur in 11% of the DMD cases [2••]. Aminoglycoside antibiotics such as gentamicin promote the insertion of alternative amino acids at the site of the mutated codon and demonstrated inconsistent increased dystrophin production and renal and otic toxicities in DMD trials [10]. Translarna (formerly Ataluren, PTC124/PTC Therapeutics) is a first-in-class compound promoting nonsense read through. Following pre-clinical studies in *mdx* mice [11], a mouse model for DMD [1••], translarna was shown to be well-tolerated in patients. A Phase 2b trial demonstrated a slower disease progression and a non-significant improvement in a six minute walk test (6MWT) and served as the basis for EMA approval in July 2014. Unfortunately, a confirmatory Phase 3 clinical trial in 228 ambulatory DMD patients demonstrated a non-significant benefit in the 6MWT. Although PTC Therapeutics recently decided to discontinue current clinical development of ataluren in cystic fibrosis, the FDA has granted orphan drug designation to translarna and discussions are in progress for approval for DMD. Another read-through compound arbekacin sulfate NPC-14 acting as a protein 30S ribosomal subunit inhibitor is in a phase 2 trial in Japan. Other compounds such as the nonaminoglycoside RTC13/RTC14 [12] and the gentamicin derivatives NB74 and NB84 show increased read-through efficacy and reduced toxicity in *mdx* myotubes [13] but have not yet been tested in patients.

Utrophin

Utrophin is a structural and functional autosomal paralogue of dystrophin which shares 80% of homology with dystrophin and has functional redundancy [14].