Will oral therapies be eclipsed by parenteral delivery in the treatment of restless legs syndrome?

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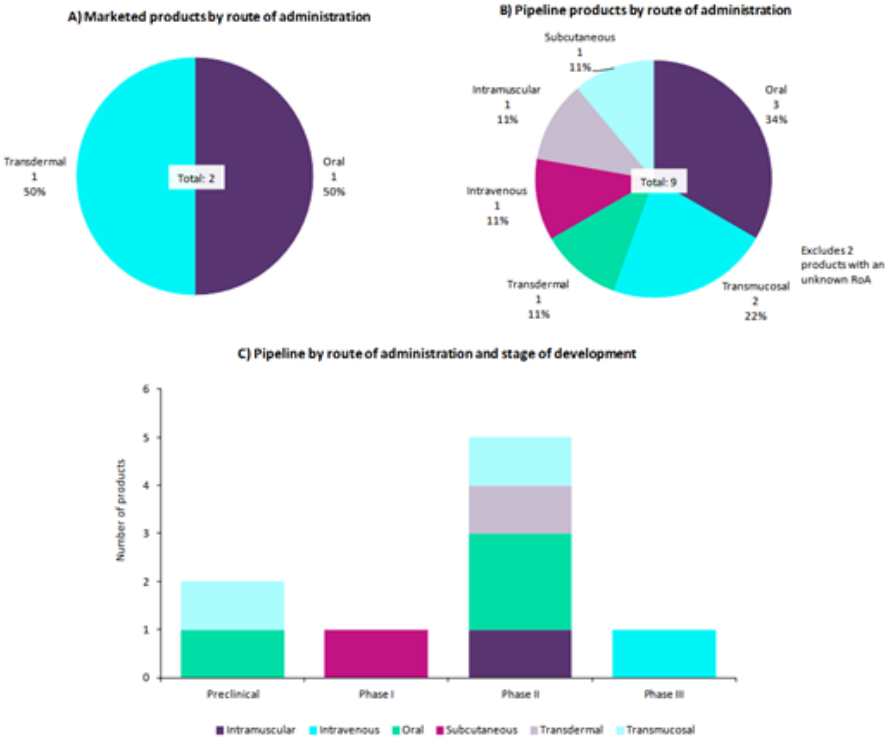
Restless legs syndrome (RLS) is a neurological movement disorder that affects more than 37 million people worldwide. The disorder is principally characterised by feelings of discomfort when the legs are stationary. This feeling is briefly relieved upon moving the legs and most noticeably affects patients when they are trying to sleep.

There are currently two US Food and Drug Administration-approved therapies for RLS, Mirapex (pramipexole dihydrochloride) and Neupro (rotigotine). Mirapex is delivered in tablet form, taken orally once daily, and Neupro is a patch that, when attached to the skin, delivers rotigotine, a dopamine receptor agonist, over a 24-hour period.

While oral treatments often have advantages such as simple dosing arrangements, portability, and the convenience of being able to take tablets without medical supervision, common problems are pharmacokinetic in nature. For example, first-pass metabolism often degrades tablets before they can pass the blood-brain barrier and exhibit therapeutic effects. In RLS, it is essential that drugs reach the brain as neuromuscular junctions, neurotransmitter receptors, and nerve terminals are frequently used as molecular targets for medications to provide symptomatic relief.

The pipeline for RLS features three products that are taken orally. However, there are five other drug candidates with different routes of administration (ROAs) being trialled, including subcutaneous, intramuscular, and transmucosal delivery. The graphs below display the marketed and pipeline products for RLS by ROA.

RLS marketed and pipeline products by route of administration, June 2019



Source: GlobalData, Pharma Intelligence Center, accessed 4 June 2019

The highest stage of development represented in the pipeline is Phase III, and this product is Vifor Pharma's Ferinject (ferric carboxymaltose), an intravenously administered iron replacement therapy. A commonly experienced comorbidity of RLS is anaemia, caused by iron deficiency. Fewer circulating erythrocytes reduce dopaminergic signalling capabilities, triggering restlessness and disordered involuntary movements. Iron replacement therapy has been proven to be effective in relieving RLS symptoms. In addition, 66.7% of drug candidates at Phase II or above are not delivered via the oral route of administration.

As a prevalent movement disorder, common symptoms of RLS include fatigue, involuntary muscle twitches, depression and irritability and can have significant negative impacts on patients' quality of life. In addition, as a highly comorbid condition, RLS is commonly linked to disorders of metabolism such as uremia and diabetes.

The sparse landscape of the RLS marketplace mean that patients are sometimes left untreated and can suffer severe consequences resulting from electrolyte imbalances and deficiency of essential nutrients such as folate and vitamin D. The differences between the routes of administration being trialled in the pipeline and the limited delivery systems available in marketed therapies are reflective of the steady innovation for this indication that recognises the need to accommodate a wider range of patients suffering from this physically challenging neuromuscular disorder.