

**SPRAYS FOR PAIN MANAGEMENT AS AN ALTERNATIVE TO
INJECTION AND OTHER ROUTES OF ADMINISTRATION**



■ ■ A scientific roundtable hosted by Aptar Pharma Prescription Division

■ ■ INTRODUCTION AND OBJECTIVES

- Aptar Pharma recently hosted a scientific roundtable on “Sprays for pain management as an alternative to injection and other routes of administration”. This international scientific forum was held in Paris, France on October 4th 2011. The roundtable was organized to explore and exchange views on the science of pain management and its related unmet medical needs.

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Sprays offer numerous advantages in the field of pain management including a non-invasive mode of delivery, fast onset of action, short duration of action, and avoidance of gastrointestinal first pass metabolism. They are suitable for out-patient use and offer superior relief of acute pain compared with oral products³. However some challenges remain to be resolved including optimizing self-titration and minimizing the possibility of overdose.

The overall objectives of the meeting were to better understand science and medical needs with regard to pain management, establish current and future unmet medical needs, and identify potential opportunities for nasal or buccal spray treatments in this area.

During this one day meeting the experts shared their knowledge and debated several key themes, structured around the following subject areas:

- Optimal pharmacokinetic profiles versus specific pain treatment requirements
- Drugs, therapies and patient needs
- Unmet medical needs

Invited guests came from a variety of backgrounds ranging from front-line clinicians to leading pharmaceutical company experts as well as participants specialized in nasal drug delivery. All held senior positions either within the industry or in hospitals, and many were recognized key opinion leaders.

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We would like to thank our guests for their excellent contributions to the roundtable and for helping to make the event both informative and enjoyable.



■ ■ CLASSIFICATION OF PAIN

- Pain is classified primarily according to duration and severity, patient outlook and treatment options.

Acute pain can be of varying severity, primarily caused by nociceptive or neuropathic mechanisms and associated with a large number of different causes, for example:

- Breakthrough pain - abrupt, short lived and intense pain experienced widely by cancer patients. It can occur in malignant and non-malignant disease.
- Post-operative pain - a complex response to tissue trauma after surgery that stimulates hypersensitivity to the central nervous system. It can be felt after trauma or any surgical procedure, whether minor or major.

The cause of acute pain can usually be diagnosed and treated, and the pain is self-limiting. Acute pain generally resolves within the normal expected healing period. The British Pain Society defines acute pain as short-term pain of less than 12 weeks' duration¹.

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Chronic pain is defined as persisting over a longer period¹ (> 3 months), even after tissue damage has healed. If acute pain is not adequately treated, it may lead to the development of harder-to-treat chronic pain.



■ ■ OPTIMAL PK PROFILES FOR BREAKTHROUGH PAIN MANAGEMENT

■ One example of acute pain is BTCP (breakthrough cancer pain) where the textbook definition is “a transitory exacerbation of pain experienced by a patient who has relatively stable and adequately controlled background pain”², see **Figure 1**. It is a particularly difficult class of pain to treat as it has a rapid onset (median ~3 minutes to peak intensity), it has a relatively short duration (~30 minutes) and a median daily frequency of 4 episodes.

The ideal breakthrough pain treatment^{3,4} should be effective, have a fast onset of action and a short duration of effect, have minimal adverse effects and should be easy and convenient to administer, see **Figure 2**. Today’s treatment of choice for BTCP, oral morphine, is not the optimal choice since the time of onset of pain relief is 30–40 minutes post-dosing, it has a long duration of action (4 hours), it increases the risk of side effects and in addition patients may have problems with swallowing during BTCP.

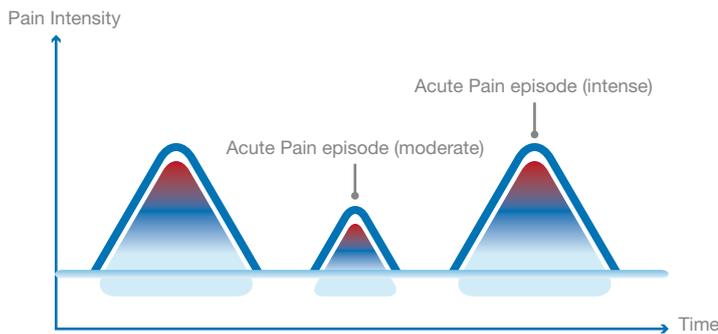


Figure 1: Typical Cancer Pain

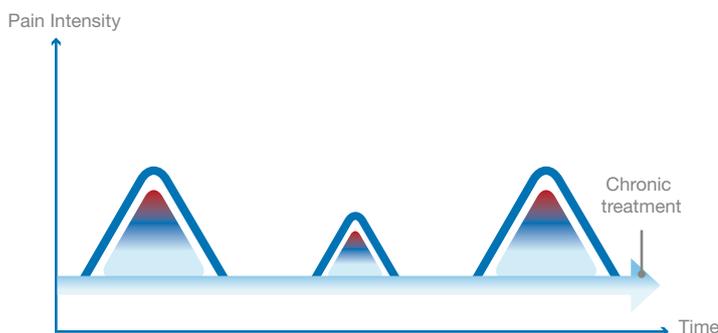


Figure 2: Background Cancer Pain Treatment

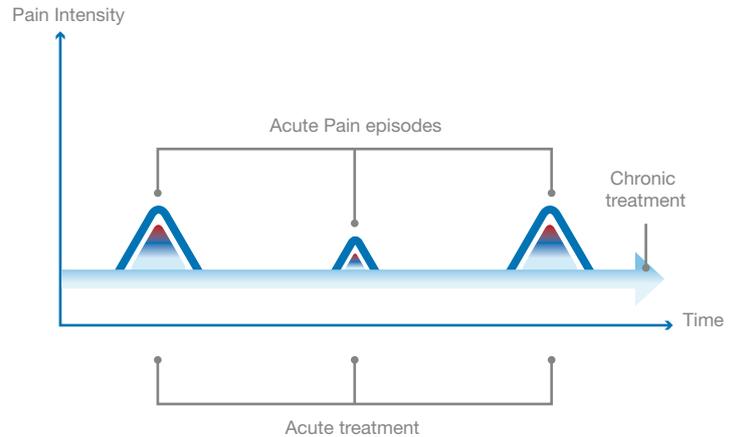


Figure 3: Ideal Breakthrough Pain Treatment

Discussions around the table clearly identified intranasal drug administration of a fast absorbing analgesic with a short half-life as ideal for this kind of pain therapy. There have been two therapies recently added to the marketplace which address most of the above requirements, namely Instanyl® (Nycomed GmbH) and PecFent®/Lazanda® (Archimedes Ltd). These therapies contain fentanyl, a strong fast acting analgesic (100 times more potent than morphine) with a short half-life, which is rapidly absorbed through the epithelium following intranasal delivery with a spray device. There is now significant data to support the benefits of these new products - for example, intranasal fentanyl, Instanyl®, has been proven pharmacokinetically to have a fast onset of action^{5,6,7} is easy for patients to use⁶ and is well tolerated⁷.

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Clearly much progress has been made in the area of better matching the PK profiles of therapies for pain management such as BTCP, and in discussions it became clear that this is a growing area of interest for pharmaceutical companies, with recent market launches and several promising products in development for either nasal or sublingual pain management therapies.

■ ■ DRUG, THERAPIES AND PATIENT NEEDS

- Opioids still seem to be the mainstay in pain treatment: drug therapy usually starts with non-narcotic analgesics and NSAIDs (non steroidal anti-inflammatory drugs), then mild opioids, followed by stronger opioids. Moderate to severe pain is typically only managed adequately by strong opioids, e.g. morphine, oxycodone, hydrocodone, fentanyl and oxycodone.

Overall it was agreed that there is still a gap with regard to clinicians having the appropriate indication of medicines to treat all levels of pain adequately for their patients. In terms of the current evolution of pain therapies, it appears that around 60% of 'new' treatments are re-formulations of existing drugs with novel delivery methods, the other 40% of potentially new therapies coming from the areas of combination drugs (active pain therapy with co-drug to minimize its side effects) and 'novel drug mechanisms' to treat pain.

■ ■ UNMET MEDICAL NEEDS

- This subject generated much discussion and it became clear that there is a lack of well matched therapy to manage some classes of pain, for example back pain. Studies have revealed that the median time to onset of meaningful pain relief was significantly shorter in patients receiving OTFC (oral transmucosal fentanyl citrate), about 15 minutes, than in patients receiving oral opioids via the gastrointestinal path, more than 30

Spray devices with their quick onset of action coupled with sustained release formulations could be a way forward

minutes⁸. Similarly, it was noted that meaningful pain relief was achieved in 11 minutes for intranasal fentanyl⁹. Often unmet medical needs are linked to clinician concerns about adverse effects and tolerance as well as addiction. All agreed that a major step forward could be achieved in unmet medical needs if there were products available which could minimize side effects of current pain management therapies. Some of the key side effects noted were nausea and vomiting, drowsiness, itching, dry mouth, miosis, and constipation. There was also comment that education of patients to help them better evaluate their pain and their feelings after taking a drug would help optimize pain therapy substantially.

All these elements taken together offer the possibility to improve pain management as they would tackle the lack of appropriate dosages linked to personalized therapy,

and treatment could be adapted to each patient's pain profile and needs. Safety (and side effect) issues and abuse liabilities could well be resolved from the delivery device perspective, and opportunities clearly exist for novel devices, such as devices fitted with electronic add-ons which could provide useful functions such as lock-out and dose counting. On the formulation side, spray devices with their quick onset of action coupled with sustained release formulations or delivery systems could be a way forward and exciting possibilities exist in this area.



■ ■ IN SUMMARY

Pain is generally well classified but individual patient perception of pain levels are still not easy to interpret precisely.

There are significant unmet medical needs in the pain management field, notably in providing optimal PK profiles for therapies in the acute pain area and also in minimizing side effects of current pain management therapies.

There is an overall gap with regard to clinicians having the appropriate indications of medicines to treat all levels of pain adapted to meet individual patient needs.

Many opportunities for improved pain management therapies exist and some of these can be achieved by improvements in new drugs with fewer side effects.

Exciting possibilities also exist for new drug delivery devices (incorporating add-on safety features) coupled with improved formulations tailored to meet specific pain management needs.

■ ■ SOME QUOTES FROM OUR EXPERTS

« The nasal route is a fascinating topic because it is non-invasive and it is surprisingly close to intravenous with regard to pharmacokinetic profile. »

« Fascinating symposium with an audience from many disciplines which led to many open and interesting scientific discussions. »

« It appears there are many opportunities available in this area of non-invasive pain management. »

■ ■ PARTICIPANTS

Dr Sebastiano Mercadante, Professor of Palliative Medicine, University of Palermo, Italy

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Dr Steve Newman, Scientific Consultant and founder of Pharmaceutical Profiles Ltd, UK

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Dr Dic Williams, Formerly Research Fellow, Pain Management at Pfizer, UK

Dr Gerallt Williams, Director, Scientific Affairs, Aptar Pharma, France



The summary of some of the discussions held, detailed above, reflects the views of our invited experts and every attempt has been made to reflect the overall consensus of view as accurately as possible.

■ ■ REFERENCES

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