Once an effective dose has been determined, sustained pain relief generally relies on a routine of administration that only varies slightly to accommodate transient changes in lifestyle (level of exercise for example) or circumstances (maybe an event such as a wedding to attend, perhaps, or a long journey).

However, there may be changes in the side-effects which emerge over time and also the underlying causative condition may worsen, thereby necessitating re-evaluation of the dosage.

Adjunctive medication may assist with stubborn pain.

NMDA-ENHANCED ANALGESIA:

Clinical trials have established that a combination of morphine and dextromethorphan (an NMDA antagonist available in the United States over the counter as a cough medicine) is more effective than morphine alone.

Dr. Nathaniel Katz at the Brigham and Women's Hospital in Boston and Assistant Professor of Anesthetics at Havard Medical School, has reported results of clinical trials using morphine sulphate: dextromethorphan(MS:DM) at a ratio of 1:1.

Phase I/II safety studies showed that adding dextromethorphan does not seem to compromise the safety of morphine nor enhance the addictive potential. However, MS:DM has a rapid onset with peak blood levels at one hour (like morphine sulphate alone) and on average, studies have found that patients experience satisfactory pain relief with half the dose of morphine, when

using MS:DM, which is known as Morphidex.

Trials have also shown that there is no increased incidence of adverse effects. A study by Goldblum for Algos, the manufacturers of Morphidex, suggests that long-term use (more than 6 months, some 200 patients treated for over 1 year) showed that there were no clinically significant treatment-related changes in laboratory tests or neurological examinations.

Adverse effects were broadly similar to those seen in all opiate preparations, the incidence being greatest during the first month of treatment and decreasing over time (except for constipation.)

Chevlen's study at Youngstown ([i]) found that doses remained constant over 10 months, suggesting that tolerance did not develop in that time.

Katz has found that most patients express much higher satisfaction with MS:DM than with morphine alone and prefer MS:DM to morphine as a "run-in" medication. Morphidex also has a longer duration of action than morphine (6-8 hours as compared with 3-4).

CCK ANTAGONISTS:

Animal studies have suggested that the anti-opioid peptide cholecystokinin (CCK) is implicated in neuropathic pain and that neural damage raises plasma CCK.

Administering a CCK antagonist such as proglumide may render neuropathic pain more responsive to opiate medication.

In addition, it has been found that in chronic opiate use, CCK levels may be raised which can work against the analgesic effect of the opiates, contributing to the tolerance that may develop; using drugs like proglumide may help to reverse this aspect of tolerance.

A study by Bernstein et al ([ii]) looked at use of proglumide in cancer patients being treated with opiates. Usual medication levels were alternated on different days with half the normal dose given simultaneously with 50mcg proglumide.

This regime was found to be effective and to produce considerably less sedation than morphine alone and there was no toxicity found with the proglumide administration. CCK antagonists may therefore be useful as adjuncts in opiate therapy for neuropathic pain.

---

[i] Chevlen E, *J Pain Symptom Manage* 2000 Jan;19 (1 Suppl):S42-9 Morphine with dextromethorphan: conversion from other opioid analgesics

[ii] Bernstein ZP et al, *J Pain Symptom Manage* 1998 15(5):314-320 Proglumide as a morphine adjunct in cancer pain management