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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

COMPOUNDING FOR THE MANAGEMENT OF PAIN

INTRODUCTION

Pain—both complex and perplexing, affects every person in the world at some time or other. Next to the common cold, pain is the reason patients seek a healthcare practitioner. One of the most prevalent, challenging and influential problems facing our modern society is chronic pain. Statistics related to the incidence of pain are phenomenal but do not tell the entire story, as many of those affected are family, friends and employers of those experiencing the pain. While most individuals experience acute, mild to moderate pain, some individuals experience chronic, severe pain. In 1987, it was estimated that more than 75 million Americans suffer from chronic, handicapping pain; many typically suffering through several years of agony, undergoing two or more failed surgeries for pain relief, are employment restricted, experience chronic sleep disturbance and marital/family dysfunction, suffer from depression and emotional distress or are physically and psychologically depleted.[1,2] In 1999, it was reported that the world market for analgesics was about $7.7 billion (US currency) and increasing at a rate of 7% annually; Americans spend about $3 billion annually on nonprescription analgesics. The total cost of "pain" in the US is estimated to be in excess of $100 billion annually.

While it is true that patients do not die from benign pain, many patients suffer needlessly and experience a disabling and pleasureless existence. It substantially impacts an individual's psychological, social, vocational, behavioral and physical well-being. Some severely afflicted chronic pain patients sadly do not look forward to a long life; rather, they anxiously await an end to their suffering. The impact of unrelieved chronic pain can result in a decreased quality of life, functionality, activity, appetite, productivity, earned wages and a willingness to be compliant with medical therapy. It can also increase patient/family financial burden, hospital costs, the number and duration of hospitalizations, pain and suffering and suicidal tendencies if the pain becomes intolerable.

Pain is generally undertreated by most healthcare professionals. This is especially true when it involves the use of opioids. Why is it that despite the scientific and clinical methods available, many health care practitioners continue to deny the use of opioid analgesics to patients in severe and unrelenting pain? Pain is the single most feared symptom for patients that are diagnosed with cancer. Tremendous strides have been made, but, an unacceptably large number of patients still do not receive adequate pain relief. It is now time to educate health care practitioners and patients with the newer knowledge available and change attitudes and healthcare practices for pain patients.

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A BRIEF HISTORY OF PAIN TREATMENT

The Chinese introduced acupuncture about 4,500 years ago; this was followed by the use of herbs and, specifically, opium. Opium and alcohol have been routinely used as analgesics in most cultures. In approximately 2600 BC and until the 18th century, acupuncture, massage, exercise, opium, alcohol, herbs, witch doctors, medicine men, prayer, exorcism, sacrifices and religious ceremonies were used. Mesmerism and electrotherapy were introduced in the 18th century. The 19th century introduced nitrous oxide, hypnosis, Muller's specificity theory, morphine, codeine, aspirin, diethyl ether, cocaine, papaverine, physical therapy, hydrotherapy, thermotherapy, mechanotherapy and electrotherapy. Our current century finds procaine, lobotomy, gate control theory, dorsal column stimulation, transcutaneous electrical nerve stimulation (TENS), biofeedback, operant conditioning, pain clinics, neurotomy/neurectomy, anesthetics, narcotic agonists/antagonists, nonsteroidal anti-inflammatory agents (NSAIDS), steroids, thalamic stimulation and serotonin-altering drugs.[3]

TRANSITIONING INTO THE NEW MILLENNIUM

Over the past fifty years, "modern" pain management has involved the use of relatively conservative approaches using pharmacological agents such as salicylates (aspirin), acetaminophen, opiates (codeine, morphine), NSAIDS (ibuprofen, etc.) and the newer synthetic narcotics (fentanyl, etc.). Large doses of opiates, however, were not prescribed due to the fear of "addicting" the individual to the drug and potential legal implications. Recently, however, it has become apparent that high doses of morphine can be safely used to enhance the quality of life of those experiencing severe, chronic pain.

Routes of administration have historically been limited to oral and parenteral. Today, however, pain management also makes use of rectal, topical, nasal and respiratory routes of administration. Formerly, dosage forms were primarily limited to tablets, capsules, injectables and suppositories. Today, however, transdermal patches, gels, sprays, inhalations, gummy gels, troches, sublingual drops, etc. are commonly used.

As is evident from this brief history and introduction, the past 5 years has seen a dramatic change in the philosophy of treating pain and in the approach to managing pain. Since, in many cases, there are no commercially available products, it is important that compounding pharmacists be a part of any pain management program. A compounding pharmacist can assist the practitioner in individualizing medications, dosages, dosage forms and enhancing patient compliance.

THE MECHANISM OF PAIN

The mechanism of a painful experience can begin with a noxious stimuli (chemical, mechanical, thermal) causing tissue injury to the skin, muscle or viscera, called nociceptive pain. Electrical impulses are generated and transmitted from this site to specific centers in the brain. This sequence of events, called nociception, results in the perception of pain. Nociception involves four processes; transduction, transmission, modulation and perception.

When the noxious stimuli results in tissue injury, endogenous chemical mediators are released or synthesized and will directly stimulate inflammatory mechanisms which enhance transduction. Histamine, bradykinin, cytokines, substance P, serotonin and prostaglandins can be involved in the various inflammatory processes. For example, prostaglandins, which are synthesized from arachidonic acid by cyclooxygenase, are associated with an inflammatory response and can induce an enhanced, prolonged response to pain known as hyperalgesia. The NSAIDS inhibit prostaglandin synthesis and will relieve this type of pain.[4]

Specific receptors, termed the opioid receptors, are located in the brain, spinal cord, adrenal medulla and peripheral nerves. These receptors are called the mu (μ), kappa (κ), sigma (σ), delta (δ) and epsilon(ε) receptors. Each receptor can elicit a specific spectrum of pharmacologic activity and different receptors can be associated with different analgesics. There are two types of μ receptors, μ1 and μ2. The former induces analgesic effects and the latter can induce side effects, such as respiratory depression. The currently used opioids (opioid agonists) induce both effects and activate both μ receptors, i.e., induce analgesia as well as respiratory depression.[4] The opioids also inhibit substance P, resulting in pain relief.[4]

Pain resulting from an injury to the peripheral or central nervous system is called neuropathic pain. Neuropathic pain is often described as sharp and burning whereas nociceptive pain is often described as dull and aching and is somatic pain (originating from the skin, bones or muscles) or visceral pain (coming from the abdominal or thoracic organs).

Another type of pain, idiopathic pain, is a nonspecific pain with an unknown origin. Stress, anxiety and depression can influence this type of pain, which is usually located in the head, neck, shoulders, abdomen and pelvic areas.

CLASSIFICATION OF PAIN

It helps to classify the type of pain experienced in order to develop an appropriate pain management program. Pain is subjective; consequently, the only real way to assess it is by the patient's report. Pain is often classified according to its location (anatomy), intensity, underlying cause, frequency, duration and time course. Also, it should be remembered that some types of pain cannot be easily classified.

Pain is often described by its location, especially benign nonmalignant pain that does not directly threaten life but causes discomfort to the patient. Examples would be head (headache), back, pelvis, leg, foot, toe pain, etc.

Pain intensity is often described as mild, moderate, severe and excruciating. It is often placed on a scale (visual analog scale, VAS) of 1 to 10 (with 10 being the worst imaginable pain). Intensity, however, is possibly the least reliable system for classifying pain as intensity varies over time and is subjective. However, it does assist in communicating the degree of discomfort experienced by the patient.

Pain due to different underlying causes (cancer, noncancer) may be handled differently. For example, pain in a terminal cancer patient may be managed for the patient to enhance the quality of life with or without efforts to eliminate the causative disease (depending upon the severity and progression of the cancer). Noncancer pain may be treated by eliminating the causative disease/injury while simultaneously providing palliative pain management.

The most obvious method of classifying pain is by frequency/duration/time course, i.e., the temporal considerations. Generally, *acute pain* is that lasting less than 30 days and *chronic pain* is that lasting more than 6 months. The term *subacute pain* is used for the interval in-between. Acute pain generally serves a protective purpose, i.e., it warns of danger, limits utilization of an injured or diseased body part and signals the "healing process" when the pain subsides. Chronic pain does not have the significant protective effect, can last beyond the normal healing of an injury or disease and can ultimately interfere with a productive life. Some patients learn to cope with chronic pain and others require pain management. Chronic pain can be further divided into benign and cancer-related.

Two other pain types are used. First is the "recurrent acute pain" that is a pain pattern that lasts over an extended time period but recurs as isolated pain episodes. It may be an acute flare-up of a disorder and is exemplified by headache, gastrointestinal motility disorders, degenerative disc and joint disease, etc. The second is "subacute pain" which is similar to acute pain in its mechanisms. It may be the last treatment opportunity for a full restoration and a pain-free existence because once the pain has been established for more than about 6 months, the prospect of relief is minimal.

It is also helpful, when selecting the pharmacologic agent, to classify the pain according to the pathogenic mechanism, as the following 5 categories describe. (1) Nociceptor pain involves specialized sensory nerve endings excited by pathophysiological processes.[5] (2) Neuropathic pain involves afferent fibers directly responding to stimuli after damage by compression or chemical involvement. (3) Deafferentation pain occurs when neurons in the central nervous system become hyperexcitable after a loss of sensory input. (4) Reactive pain is nociceptor excitation by dysfunctional motor or sympathetic efferent or reflex mechanisms. (5) Psychosomatic pain is involved when psychic or psychosocial problems aggravate existing pain or are expressed in the language of pain. It is important to know the pathogenesis of the pain in the selection of the appropriate pharmacologic agent.

In summary, the objective classification of the subjective pain experience is difficult. The pain experience is universal and probably the most common impetus for patients to seek professional healthcare. Even though somewhat arbitrary and subjective, its classification is a step towards appropriate pain management.

NOCICEPTOR VS NEUROPATHIC PAIN: GENERAL TREATMENT CONSIDERATIONS

In selecting a treatment regimen, it is important to distinguish between nociceptor pain (transmitted over intact neural pathways) and neuropathic pain (related to damaged neural strictures, often involving neural supersensitivity).

Nociceptor pain, depending upon its severity, generally responds to the common analgesics; aspirin, acetaminophen, NSAIDs, opiates, etc. The doses required are dependent upon the severity of the pain. Generally, oral dosage forms are used except as previously noted.

Some follow a general guideline for nociceptor pain; NSAIDS for mild pain, NSAIDS plus low-dose opioids for moderate pain and NSAIDS plus higher doses of opioids for severe pain.[6]

Neuropathic pain includes trigeminal neuralgia, postherpetic neural-

gia and diabetic neuropathy. This pain can be described as lancinating with a sharp, shooting or stabbing component; or it may be burning in nature. It may be accompanied by allodynia, or pain arising from external stimulation such as a light touch.

Neuropathic pain is usually less sensitive to opioids than nociceptive pain, but may be effective at high doses when given intraspinally. Neuropathic pain is commonly treated with such medications as tricyclics, anticonvulsants (gabapentin, carbamazepine, mexilitine), and drugs such as baclofen, lidocaine, loperamide, topical aspirin:ether, clonidine, ketamine and capsaicin.

TREATMENT

Generally, the first approach to pain management is nonpharmacologic; diet, exercise, physical medicine (heat, ice packs, massage, physical therapy). If this is not effective or appropriate, then drug therapy is indicated. Once a general classification of the pain has occurred, a treatment plan can be formulated based on the work-up; mild acute pain is treated differently than severe chronic pain. Also, if the pain is the result of a physiological disorder, drug therapy is also initiated to treat the disorder, as well as to manage the pain. Also, the therapeutic agent selected should be appropriate for the pain category of the patient. Generally, doses of a pharmacologic agent should be titrated to effectiveness.

Acute mild pain may not require treatment or may require only minimal treatment. Chronic mild pain may require treatment for the comfort of the patient. Mild pain can often be treated by nonprescription medications including aspirin, acetaminophen, and the NSAIDs (ibuprofen, naproxen sodium). These generally are initially given orally.

If not successful and the mild pain continues, the NSAIDs are easily available to the patient on a nonprescription basis. For chronic mild pain, however, many patients do not feel comfortable using the NSAIDS due to their gastrointestinal side effects. An alternative dosage form, requiring a prescription, is becoming more common so they can be administered topically in a penetrating topical vehicle. (See Formulations 1 and 2).

For moderate pain, the dose of the aspirin, acetaminophen, ibuprofen, naproxen sodium or ketoprofen can be increased. The NSAIDs would require prescriptions at these dosages in all dosage forms (oral and topical). If unsuccessful, other NSAIDs can be selected, including diclofenac, etodolac, fenoprofen, flurbiprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, nabumetone, oxaprozin, piroxicam, sulindac and tolmetin. These are commonly given orally but some of them are also routinely used in topical formulations.

For moderate pain that is still unresponsive, the combination of aspirin or acetaminophen with codeine is appropriate. Other alternatives include oxycodone with aspirin, oxycodone with acetaminophen, pentazocine and propoxyphene napsylate. If the response is still unsatisfactory, implementation of tramadol may be indicated.

For severe pain, the standard of treatment is morphine, which is an excellent narcotic analgesic since it is a pure agonist. For acute severe pain, instead of starting with a low dose and working up, it is becoming more common to start the selected drug aggressively, i.e., start high and work down, affording the patient more rapid pain relief. The tradeoff is the patient may experience some side effects initially and must be carefully monitored. Pharmacologic agents commonly used include buprenorphine, butorphanol, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, morphine extended release, nalbuphine, oxycodone, oxymorphone and pentazocine. For acute chronic pain, morphine is the drug of choice, preferably administered orally. Based upon the severity and nature of the patient's pain, doses ranging from 10 to 100 mg may be required and there are no upper limits of the dose for patients suffering from severe chronic pain. Long-acting dosage forms of morphine sulfate are commonly used in these situations. An alternative method is the use of Patient-Controlled Analgesia (PCA) pumps. These pumps can be programmed to deliver regular doses of a narcotic directly into the patient. These pumps are microprocessor controlled and can be programmed to allow the patient to dose themselves (with certain limitations) and some will even provide a printout of the doses administered. Solutions of these drugs are compounded by pharmacists and placed into the pump reservoirs / syringes / cassettes. Also, pain cocktails (Brompton's Mixture) have been used, consisting of morphine and cocaine as the primary active ingredients. A more recent therapeutic approach has been the use of epidural infusion of various drugs for chronic pain control. These infusions may include morphine sulfate, bupivacaine hydrochloride, baclofen, fentanyl citrate, hydromorphine hydrochloride and other drugs and are compounded by the pharmacist.

Generally, there is no advantage to parenteral administration over equianalgesic doses of orally administered medications. If oral dosing is not feasible, sublingual / buccal and rectal administration are alternative noninvasive routes that can be considered before injections. A few comments on using morphine. Starting morphine therapy is best done with the immediate-release tablets. Once the dose has been titrated, a slow-release formulation can then be used. Dosing is usually best done on a regular schedule around-the-clock, using PRN doses for breakthrough pain. As an example, consider morphine. Generally, a PRN dose is about 1/2 of the every 4 hour dose, (which is about 1/6 of an every 12 hour controlled release opioid dose), given every 2 hours; administered as an immediate release dosage form. If the patient requires more than 2 or 3 breakthrough doses daily for two to three days, it may be time to increase the regularly scheduled dose regimen.[6]

A good second-line drug for patients previously using opioids is methadone, due to its wide availability and relatively low cost. Oxycodone is commonly used to treat moderate-to-severe pain. A synthetic opioid often used as second line treatment in cancer patients is levorphanol, especially for those patients that cannot tolerate morphine. Fentanyl, in different dosage forms including a transdermal patch, is effectively used in cancer patients, especially with the 72 hour release profile providing sustained, effective pain relief.

Cancer pain may consist of about 10-20% neuropathic pain, being only partially responsive to opioids. Consequently, pain treatment in cancer patients also includes adjuvant analgesic drugs, including anticonvulsants, phenothiazines, butyrophenones, tricyclic antidepressants, antihistamines, amphetamines, steroids and levodopa. These agents can alleviate pain by mechanisms that are not yet clearly understood and may not be directly related to the opiate receptor system.

In addition, N-methyl-D-aspartate (NMDA) receptors have been found to play an important role in aggravating chronic pain. NMDA receptor antagonists , such as ketamine have been used to effectively block this.

Of these miscellaneous agents that have been effectively used for various types of pain, the tricyclics may provide analgesic activity within about 5-7 days usually at slightly lower than normal antidepressant doses. Also, clonazepam has been effective in combating phantom limb pain, dosed at 0.5 mg three times daily. It can also be used in combination with a tricyclic in neuropathic pain.

Minor chronic muscle pain is often treated orally and topically with the use of analgesic agents, including the counterirritants (methyl salicylate, capsaicin) and the NSAIDS in penetrating-enhancing formulas.

Choline magnesium trisalicylate and salsalate do not significantly affect platelet aggregation and can be used as the NSAIDS of choice for thrombocytopenic patients or patients with bleeding disorders.

Colchicine has been used, both intravenously and orally, for many painful disorders including post zoster neuralgia, rheumatoid arthritis, gout, migraines, cluster headaches, neuralgias, phantom limb pain, sinusitis, and numerous other conditions.[7]

Anesthetics, both short-acting and long-acting, can be used for temporary and diagnostic nerve blocks. Phenol, alcohol and freezing (cryoanalgesia) are neurolytics that can be used for permanent blocks. The continuous or intermittent epidural infusion of local anesthetics have been used in difficult to control pain management cases. Trigger-point injections of either saline or a local anesthetic can provide relief.

In a dying cancer patient, nitrous oxide has been used to manage severe, chronic pain resulting from tumor progression. Bone pain, from skeletal metastases, can be treated with bisphosphonates. Sublingual 0.1 mg buprenorphine troches have been effective in some patients with fibromyalgia.

Many new combinations of topical agents are being used. It is important to generally, continue therapy for about one week before assessing the response. It is generally advisable to use the highest reasonable and safe dose of topicals to begin and then adjust accordingly. Agents often used topically include aspirin, capsaicin, clonidine, desipramine, DMSO, gabapentin, guaifenesin, guanethidine, ketamine, local anesthetics (lidocaine) and the NSAIDs.

CO-ANALGESICS

Many of the drugs previously mentioned serve as co-analgesics. Co-analgesics are agents that have not been primarily used for their analgesic properties but have been found to be effective, either alone or in combination with other drugs, to relieve pain. Examples include the tricyclic antidepressants (amitriptyline, nortriptyline, imipramine, desipramine, doxepin) where the dose is generally less than that required as an antidepressant and the analgesic effect occurs sooner than the antidepressant effect. Dextromethorphan is often used in conjunction with opioids to reduce the total opioid dose. A common regimen is 30 mg three times daily for 2 days, then 60 mg three times daily as tolerated.

Others include the serotonin selective reuptake inhibitors (fluoxetine, paroxetine, sertraline), anticonvulsants (carbamazepine, clonazepam, gabapentin, phenytoin, valproic acid), antiarrhythmics (mexiletine, tocainide, lidocaine), alpha-1 antagonists (phenoxybenzamine, prazosin, phentolamine) and the alpha-2 agonist (clonidine-epidurally or intrathecally).

COMPOUNDED FORMULATIONS FOR PAIN MANAGEMENT

Solution Examples:

Rx Aspirin 50 mg / mL in Ether Topical Solution

Aspirin		500 mg
Ether		10 mL

Add the aspirin and the ether to a glass container, cap and mix well. Keep tightly closed. Package and label.

Rx Dexamethasone and Lidocaine Solution for Iontophoresis

Dexamethasone sodium phosphate		400 mg
Lidocaine hydrochloride		1 g
Sterile water for injection	qs	100 mL

Dissolve the dexamethasone sodium phosphate and the lidocaine hydrochloride in the sterile water for injection. Sterile filter into a sterile container. Package and label.

Rx Morphine Sulfate 10 mg / mL Inhalation Solution

Morphine sulfate		1 g
Citric acid, hydrous		100 mg
Sterile water for injection	qs	100 mL

Dissolve the morphine sulfate and the citric acid in about 90 mL of sterile water for injection. Add sufficient sterile water for injection to volume. Sterile filter into a sterile container. Package and label.

Topical Gel (Pluronic-Lecithin Organogel) Examples:

Rx Amitriptyline Hydrochloride 2% in PLO

Amitriptyline hydrochloride		2 g
Ethanol, 95%		5 mL
Lecithin / Isopropyl palmitate solution		22 mL
Pluronic F-127 20% gel	qs	100 mL

Mix the amitriptyline hydrochloride with the alcohol to form a smooth paste. Add the lecithin:isopropyl palmitate solution and mix well. Add sufficient Pluronic F-127 gel to volume and mix well. Package and label.

Rx Capsaicin and Ketamine Hydrochloride in PLO

Capsaicin		50 mg
Ketamine hydrochloride		2 g
Ethanol, 95%		5 mL
Lecithin / Isopropyl palmitate solution		22 mL
Pluronic F-127 20% gel	qs	100 mL

Mix the capsaicin and the ketamine hydrochloride with the alcohol to form a smooth paste. Add the lecithin:isopropyl palmitate solution and mix well. Add sufficient Pluronic F-127 gel to volume and mix well. Package and label.

Topical Cream Examples:

Rx Guaifenesin 10% Cream

Guaifenesin		10 g
Glycerin		5 mL
Dermabase	qs	100 g

Mix the guaifenesin with about 5 mL of glycerin to form a smooth paste. Geometrically, add Dermabase to final weight and mix well. Package and label.

Rx Hydrocortisone Cream for Phonophoresis

Hydrocortisone, micronized	10 g
Glycerin	5 g
Dermabase	85 g

Mix the hydrocortisone with the glycerin to form a smooth paste. Carefully without incorporating any air into the preparation, geometrically mix the hydrocortisone:glycerin mixture into the Dermabase until uniform. Package and label.

Medication Stick Example:

Rx Analgesic Medication Stick with Capsaicin

Methyl salicylate	25 g
Menthol	10 g
Capsaicin	25 mg
Sodium stearate	17 g
Purified water	15 g
Propylene glycol	33 g

Mix the sodium stearate, purified water and propylene glycol and melt, mix thoroughly add the capsaicin and mix well. Remove from heat and allow to cool slightly. Dissolve the menthol in the methyl salicylate and add to the molten mixture just before it begins to thicken. Pour into medication stick containers and allow to harden. Package and label.

Troche Examples:

Rx Morphine Sulfate 15 mg Troche (#24, 1 g troches)

Morphine sulfate	360 mg
Aspartame	400 mg
Citric acid monohydrate	500 mg
Silica gel	600 mg
Acacia	350 mg
Polyethylene glycol 1500	21.79 g

Mix the morphine sulfate, aspartame, citric acid monohydrate, silica gel and acacia in a mortar. Melt the polyethylene glycol over low heat to about 55ºC. Remove from the heat source, add the powders and mix well. After cooling for a few minutes and while still fluid, add a flavor, if desired. Pour into molds and allow to harden. Package and label.

Rx Buprenorphine 0.1 mg Troches (#24, 1 g troches)

Buprenorphine	2.4 mg (2.6 mg buprenorphine HCl)
Aspartame	400 mg
Citric acid monohydrate	500 mg
Silica gel	600 mg
Acacia	350 mg
Polyethylene glycol 1500	22.20 g

Mix the aspartame, citric acid monohydrate, silica gel and acacia in a mortar. Melt the polyethylene glycol over low heat to about 55C. Remove from the heat source, add the powders and the buprenorphine HCl (injection) and mix well. After cooling for a few minutes and while still fluid, add a flavor if desired. Pour into molds and allow to harden. Package and label

Capsule Example:

Rx Morphine sulfate 15 mg and Dextromethorphan hydrobromide 30 mg capsules

Morphine sulfate	1.5 g
Dextromethorphan hydrobromide	3 g
Lactose	35 g

Note: It may be necessary to adjust the quantity of lactose used, depending upon its powder density. Reduce the particle size of the powders, if necessary, then mix the powders well. Encapsulate into 100 No. 1 capsules, each containing 395 mg of powder blend. Package and label.

Intrathecal Solution:

Rx Morphine sulfate 30 mg / mL solution intrathecal solution

Morphine sulfate		600 mg
0.9% Sodium chloride injection		12.7 mL
Sterile water for injection	qs	7.3 mL

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SUGGESTED READING

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NOTES:

Extemporaneous Formulations and Stability Studies Available For:

- Acetazolamide
- Allopurinol
- Alprazolam
- Azathioprine
- Baclofen
- Bethanechol
- Captopril
- Chloroquine Phosphate
- Cisapride
- Clonazepam
- Diltiazem HCl
- Dipyridamole
- Enalapril Maleate
- Flecainide Acetate
- Flucytosine
- Hydralazine HCl
- Ketoconazole
- Labetalol
- Metolazone
- Metoprolol Tartrate
- Metronidazole
- Procainamide
- Pyrazinamide
- Quinidine Sulfate
- Rifampin
- Spironolactone
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- Tetracycline HCl
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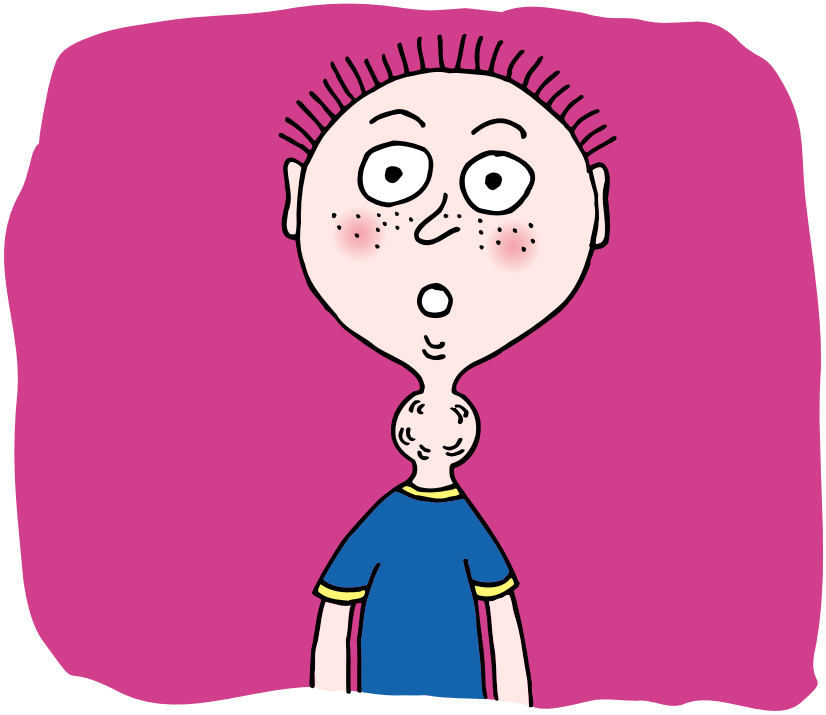

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