Migraine and Pain Management

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Migraine

Migraine

The pain of a migraine headache can be debilitating.

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Migraine is a debilitating condition characterized by moderate to severe headaches, and nausea, about 3 times more common in women than in men.

The typical migraine headache is unilateral pain (affecting one half of the head) and pulsating in nature, lasting from 4 to 72 hours; symptoms include nausea, vomiting, photophobia (increased sensitivity to light), phonophobia (increased sensitivity to sound), and is aggravated by routine activity. Approximately one-third of people who suffer from migraine headaches perceive an aura—unusual visual, olfactory, or other sensory experiences that are a sign that the migraine will soon occur.

Initial treatment is with analgesics for the headache, an antiemetic for the nausea, and the avoidance of triggering conditions. The cause of migraine headache is unknown; the most common theory is a disorder of the serotonergic control system.

Studies of twins indicate a 60 to 65 percent genetic influence upon their propensity to develop migraine headache. Moreover, fluctuating hormone levels indicate a migraine relation: 75 percent of adult patients are women, although migraine affects approximately equal numbers of prepubescent boys and girls; propensity to migraine headache is known to disappear during pregnancy, although in some women migraines may become more frequent during pregnancy.

Classification

The International Headache Society (IHS) offers guidelines for the classification and diagnosis of migraine headaches, in a document called "The International Classification of Headache Disorders, 2nd edition" (ICHD-2). These guidelines constitute arbitrary definitions, and are not supported by scientific data.

According to ICHD-2, there are seven subclasses of migraines (some of which include further subdivisions):

- *Migraine without aura*, or *common migraine*, involves migraine headaches that are not accompanied by an aura.
- *Migraine with aura* usually involves migraine headaches accompanied by an aura. Less commonly, an aura can occur without a headache, or with a non-migraine headache. Two other varieties are *Familial hemiplegic migraine* and *Sporadic hemiplegic migraine*, in which a patient has migraines with aura and with accompanying motor weakness. If a close relative has had the same condition, it is called "familial", otherwise it is called "sporadic". Another variety is *basilar-type migraine*, where a headache and aura are accompanied by difficulty speaking, vertigo, ringing in ears, or a number of other brainstem-related symptoms, but not motor weakness.
- *Childhood periodic syndromes that are commonly precursors of migraine* include *cyclical vomiting* (occasional intense periods of vomiting), *abdominal migraine* (abdominal pain, usually accompanied by nausea), and *benign paroxysmal vertigo of childhood* (occasional attacks of vertigo).

- *Retinal migraine* involves migraine headaches accompanied by visual disturbances or even temporary blindness in one eye.
- *Complications of migraine* describe migraine headaches and/or auras that are unusually long or unusually frequent, or associated with a seizure or brain lesion.
- *Probable migraine* describes conditions that have some characteristics of migraines but where there is not enough evidence to diagnose it as a migraine with certainty.

Signs and symptoms

Migraines typically present with recurrent severe headache associated with autonomic symptoms. An aura only occurs in a small percentage of people. The severity of the pain, duration of the headache, and frequency of attacks is variable.

There are four possible phases to a migraine attack. They are listed below - not all the phases are necessarily experienced. Additionally, the phases experienced and the symptoms experienced during them can vary from one migraine attack to another in the same person:

1. The prodrome, which occurs hours or days before the headache.
2. The aura, which immediately precedes the headache.
3. The pain phase, also known as headache phase.
4. The postdrome.

Prodrome

Prodromal symptoms occur in 40–60% of those with migraines. This phase may consist of altered mood, irritability, depression or euphoria, fatigue, yawning, excessive sleepiness, craving for certain food (e.g. chocolate), stiff muscles (especially in the neck), hot ears, constipation or diarrhea, increased urination, and other visceral symptoms. These symptoms usually precede the headache phase of the migraine attack by several hours or days, and experience teaches the patient or observant family how to detect that a migraine attack is near.

Aura

For the 20–30% of migraine sufferers who experience migraine with aura, this aura comprises focal neurological phenomena that precede or accompany the attack. They appear gradually over 5 to 20 minutes and generally last fewer than 60 minutes. The headache phase of the migraine attack usually begins within 60 minutes of the end of the aura phase, but it is sometimes delayed up to several hours, and it can be missing entirely. The pain may also begin before the aura has completely subsided. Symptoms of migraine aura can be sensory or motor in nature.

Visual aura is the most common of the neurological events and can occur without any headache. There is a disturbance of vision consisting often of unformed flashes of white

and/or black or rarely of multicolored lights (photopsia) or formations of dazzling zigzag lines (scintillating scotoma; often arranged like the battlements of a castle, hence the alternative terms "fortification spectra" or "teichopsia"). Some patients complain of blurred or shimmering or cloudy vision, as though they were looking through thick or smoked glass, or, in some cases, tunnel vision and hemianopsia. For those suffering from this the prodrome is a small blurred spot that we cannot focus on. This is followed by a growing into a larger object such as a three sided square with the zig-zag line interfering with vision. This grows to a maximum size and then starts moving slowly through the field of vision until it exits the field of view. For all practical purposes the aura phase has then ended even if brain activity could be detected that would indicate an active aura.

The somatosensory aura of migraine may consist of digitolingual or cheiro-oral paresthesias, a feeling of pins-and-needles experienced in the hand and arm as well as in the nose-mouth area on the same side. The paresthesia may migrate up the arm and then extend to involve the face, lips and tongue.

Other symptoms of the aura phase can include auditory, gustatory or olfactory hallucinations, temporary dysphasia, vertigo, tingling or numbness of the face and extremities, and hypersensitivity to touch.

Oliver Sacks's book *Migraine* describes "migrainous deliria" as a result of such intense migraine aura that it is indistinguishable from "free-wheeling states of hallucinosis, illusion, or dreaming."

- Visual symptoms of migraine aura

Enhancements reminiscent of a zigzag fort structure

Negative scotoma, loss of awareness of local structures

Positive scotoma, local perception of additional structures

Mostly one-sided loss of perception

Pain

The typical migraine headache is unilateral, throbbing, and moderate to severe and can be aggravated by physical activity. Not all these features are necessary. The pain may be bilateral at the onset or start on one side and become generalized, and may occur primarily on one side or alternate sides from one attack to the next. The onset is usually gradual. The pain peaks and then subsides and usually lasts 4 to 72 hours in adults and 1 to 48 hours in children. The frequency of attacks is extremely variable, from a few in a lifetime to several a week, and the average sufferer experiences one to three headaches a month. The head pain varies greatly in intensity.

The pain of migraine is invariably accompanied by other features. Nausea occurs in almost 90 percent of patients, and vomiting occurs in about one third of patients. Many patients experience sensory hyperexcitability manifested by photophobia, phonophobia, and osmophobia and seek a dark and quiet room. Blurred vision, delirium, nasal stuffiness, diarrhea, tinnitus, polyuria, pallor, or sweating may be noted during the headache phase. There may be localized edema of the scalp or face, scalp tenderness, prominence of a vein or artery in the temple, or stiffness and tenderness of the neck. Impairment of concentration and mood are common. The extremities tend to feel cold and moist. Vertigo may be experienced; a variation of the typical migraine, called vestibular migraine, has also been described. Lightheadedness, rather than true vertigo, and a feeling of faintness may occur.

Postdrome

The effects of migraine may persist for some days after the main headache has ended. Many sufferers report a sore feeling in the area where the migraine was, and some report impaired thinking for a few days after the headache has passed. The patient may feel tired or "hungover" and have head pain, cognitive difficulties, gastrointestinal symptoms, mood changes, and weakness. According to one summary, "Some people feel unusually refreshed or euphoric after an attack, whereas others note depression and malaise."

Cause

The cause of migraines is unknown.

Triggers

A minority of migraines may be induced by triggers. While many things have been labeled as triggers, the strength and significance of these relationships are uncertain. The most common triggers quoted are stress, hunger, and fatigue; however, these equally contribute to tension headaches. A 2003 review concluded that there was no scientific evidence for an effect of tyramine on migraine. A 2005 literature review found that the available information about dietary trigger relies mostly on subjective assessments. This is in line with other reviews. A 2009 review found little evidence to corroborate the environmental triggers reported. While monosodium glutamate (MSG) is frequently reported as a dietary trigger evidence does not consistently support this.

Pathophysiology

Migraine is a neurovascular disorder. Although migraine is thought by some to be a neurological disease, in the absence of scientific evidence, this remains a hypothesis.

What initiates a migraine attack?

Migraines were once thought to be initiated exclusively by problems with blood vessels, but the vascular changes of migraines are now considered by some to be secondary to brain dysfunction, although this concept has not been supported by the evidence. This was eloquently summed up by Dodick who wrote ‘There is no disputing the role of the central nervous system in the susceptibility, modulation and expression of migraine headache and the associated affective, cognitive, sensory, and neurological symptoms and signs. However to presume that migraine is always generated from within the central nervous system, based on the available evidence, is naïve at best and unscientific at worst.The emerging evidence would suggest that just as alterations in neuronal activity can lead to downstream effects on the cerebral blood vessel, so too can changes within endothelial cells or vascular smooth muscle lead to downstream alterations in neuronal activity. Therefore, there are likely patients, and/or at least attacks in certain patients, where primarily vascular mechanisms predominate.' Some have even attempted to show that vascular changes are of no importance in migraine, but this claim is unsubstantiated

and has not been supported by scientific evidence. 'If we swing between vascular and neurogenic views of migraine, it is probably because both vascular and neurogenic mechanisms for migraine exist and are important'- J Edmeads

Where does migraine pain come from?

Arteries

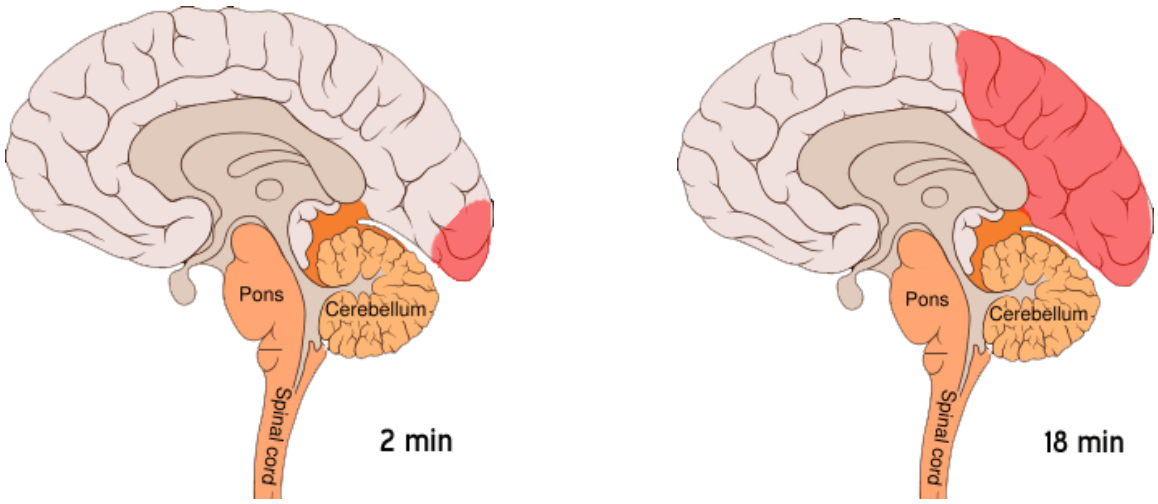
Although the initiating factor of migraine remains unknown, there is a great deal of irrefutable evidence to show that the pain of migraine (the third phase) is in some patients related to painful dilatation of the terminal branches of the external carotid artery, and in particular its superficial temporal and occipital branches. It was previously thought that dilatation of the arteries in the brain and dura mater was the origin of the vascular pain, but it has now been shown that these vessels do not dilate during migraine. Because these arteries are relatively superficial, it is easy to diagnose whether they are the source of the pain. If they are, then they are also accessible to a form of migraine surgery that is being promoted, largely to the efforts of Dr Elliot Shevel, a South African surgeon, who has reported excellent success using the procedure.

Muscles

Pericranial (jaw and neck) muscle tenderness is a common finding in migraine It has actually been shown that muscle tenderness is present in100% of migraine attacks, so muscle tenderness is the single most common finding in migraine. Tender muscle trigger points can be at least part of the cause, and perpetuate most kinds of headaches.

Migraine Hypotheses

Depolarization



Cortical spreading depression

It has been theorized that the phenomenon known as cortical spreading depression, which is associated with the aura of migraine, can cause migraines. In cortical spreading depression, neurological activity is initially activated, then depressed over an area of the cortex of the brain. It has been suggested that situation results in the release of inflammatory mediators leading to irritation of cranial nerve roots, most particularly the trigeminal nerve, which conveys the sensory information for the face and much of the head. This theory is however speculative, without any supporting evidence, and there are indeed cogent arguments against it. First, only about one third of migraineurs experience an aura, and those who do not experience aura do not have cortical spreading depression. Second, many migraineurs have a prodrome, which occurs up to three days before the aura.

Vascular relationship to the aura

Studies have shown that the aura coincides with constriction of blood vessels in the brain. This may start in the occipital lobe, in the back of the brain, as arteries spasm. The reduced flow of blood from the occipital lobe triggers the aura that some individuals who have migraines experience because the visual cortex is in the occipital area.

When the constriction of blood vessels in the brain stops and the aura subsides, the blood vessels of the scalp dilate. The walls of these blood vessels become permeable and some fluid leaks out. This leakage is recognized by pain receptors in the blood vessels of surrounding tissue. In response, the body supplies the area with chemicals which cause inflammation. With each heart beat, blood passes through this sensitive area causing a throb of pain.

Serotonin

Serotonin is a type of neurotransmitter, or "communication chemical" which passes messages between nerve cells. It helps to control mood, pain sensation, sexual behaviour, sleep, as well as dilation and constriction of the blood vessels among other things. Low serotonin levels in the brain may lead to a process of constriction and dilation of the blood vessels which trigger a migraine. Serotonergic agonists like triptans, LSD or psilocin activate serotonin receptors to stop a migraine attack.

Melanopsin receptor

A melanopsin-based receptor has been linked to the association between light sensitivity and migraine pain, but this is at this stage speculation.

Neural

When certain nerves or an area in the brain stem become irritated, a migraine begins. In response to the irritation, the body releases chemicals which cause inflammation of the blood vessels. These chemicals cause further irritation of the nerves and blood vessels

and results in pain. Substance P is one of the substances released with first irritation. Pain then increases because substance P aids in sending pain signals to the brain.

Unifying theory

Both vascular and neural influences cause migraines.

1. stress triggers changes in the brain
2. these changes cause serotonin to be released
3. blood vessels constrict and dilate
4. chemicals including substance P irritate nerves and blood vessels causing neurogenic inflammation and pain

Diagnosis

Migraines are underdiagnosed and often misdiagnosed. The diagnosis of migraine without aura, according to the International Headache Society, can be made according to the following criteria, the "5, 4, 3, 2, 1 criteria":

- **5** or more attacks. For migraine *with* aura, only two attacks are sufficient for diagnosis.
- **4** hours to **3** days in duration.
- **2** or more of the following:
    - Unilateral (affecting half the head);
    - Pulsating;
    - "Moderate or severe pain intensity";
    - "Aggravation by or causing avoidance of routine physical activity".
- **1** or more of the following:
    - "Nausea and/or vomiting";
    - Sensitivity to both light (photophobia) and sound (phonophobia).

The mnemonic POUNDing (**P**ulsating, duration of 4–72 h**O**urs, **U**nilateral, **N**ausea, **D**isabling) can help diagnose migraine. If 4 of the 5 criteria are met, then the positive likelihood ratio for diagnosing migraine is 24.

The presence of either disability, nausea or sensitivity, can diagnose migraine with:

- sensitivity of 81%
- specificity of 75%

Migraine should be differentiated from other causes of headaches such as cluster headaches. These are extremely painful, unilateral headaches of a piercing quality. The duration of the common attack is 15 minutes to three hours. Onset of an attack is rapid, and most often without the preliminary signs that are characteristic of a migraine.

Medical imaging of the head and neck may be used to rule out secondary causes of headaches.

Prevention

Preventive (also called prophylactic) treatment of migraines can be an important component of migraine management. Such treatments can take many forms, including taking preventative drugs, migraine surgery, taking nutritional supplements, lifestyle alterations such as increased exercise, and avoidance of migraine triggers, .

The goals of preventive therapy are to reduce the frequency, painfulness, and/or duration of migraines, and to increase the effectiveness of abortive therapy. Another reason to pursue these goals is to avoid medication overuse headache (MOH), otherwise known as rebound headache. This is a common problem among migraneurs, and can result in chronic daily headache.

Many of the preventive treatments are quite effective. Even with a placebo, one-quarter of patients find that their migraine frequency is reduced by half or more, and actual treatments often far exceed this figure.

Preventive or prophylactic medications

Preventive migraine drugs are considered *effective* if they reduce the frequency or severity of migraine attacks by 50%. The major problem with migraine preventive drugs, apart from their relative inefficiency, is that unpleasant side effects are common. For this reason, preventive medication is limited to patients with frequent or severe headaches.

There are many medicines available to prevent or reduce frequency, duration and severity of migraine attacks. They may also prevent complications of migraine. Beta blockers such as Propranolol, atenolol, and metoprolol, calcium channel blockers such as amlodipine, flunarizine and verapamil, the anticonvulsants sodium valproate, divalproex gabapentin and topiramate and tricyclic antidepressants are some of the commonly used drugs.

Tricyclics have been found to be more effective than SSRIs. Tricyclic antidepressants have been long established as efficacious prophylactic treatments. These drugs, however, may give rise to undesirable side effects, such as insomnia, sedation or sexual dysfunction. There is no consistent evidence that SSRI antidepressants are effective for migraine prophylaxis. While amitryptiline (Elavil) is the only tricyclic to have received FDA approval for migraine treatment, other tricyclic antidepressants are believed to act similarly and are widely prescribed, often to find one with a profile of side-effects that is acceptable to the patient. In addition to tricyclics a, the anti-depressant nefazodone may also be beneficial in the prophylaxis of migraines due to its antagonistic effects on the 5-HT2A and 5-HT2C receptors It has a more favorable side effect profile than amitriptyline, a tricyclic antidepressant commonly used for migraine prophylaxis. Anti-depressants offer advantages for treating migraine patients with comorbid depression.

Selective serotonin reuptake inhibitors (SSRIs) are not approved by the U.S. Food and Drug Administration (FDA) for treatment of migraines, but have been found to be effective by some practitioners.

Migraine surgery

Migraine surgery is a field that shows a great deal of promise, particularly in those who suffer more frequent attacks, and in those who have not had an adequate response to prophylactic medications. Patients often still experience a poor quality of life despite an aggressive regimen of pharmacotherapy. For these reasons, surgical solutions to migraines have been developed, which have excellent results. A major advantage of migraine surgery, is that with the correct diagnostic techniques, a definite diagnosis can be made before the surgery is undertaken. Once a positive diagnosis has been made, the results of surgery are outstanding and provides permanent pain relief, as well as relief from the associated symptoms such as nausea, vomiting, light sensitivity, and sound sensitivity. Surgical cauterization of the superficial blood vessels of the scalp (the terminal branches of the external carotid artery) is only carried out if the clinical examination has shown that these vessels are indeed a source of pain. It is a safe and relatively atraumatic procedure that can be performed in a day facility. The value of arterial sugery for migraine treatment is gaining recognition due to the efforts of a South African surgeon, Dr Elliot Shevel, who has produced a number of papers on the subject.

The removal of muscles or nerves in areas known as "trigger sites" provides good results, but only in patients who respond well to Botox injections in specific areas.

There is also evidence that the correction of a congenital heart defect, patent foramen ovale (PFO), reduces migraine frequency and severity. Recent studies have advised caution though in relation to PFO closure for migraines, as insufficient evidence exists to justify this dangerous procedure.

Other therapies

A systematic review stated that chiropractic manipulation, physiotherapy, massage and relaxation might be as effective as propranolol or topiramate in the prevention of migraine headaches, however the research had some problems with methodology.

Migraine diary

Keeping a migraine diary may make it possible to identify food triggers, and therefore help to avoid them.. Controlling the intake of foods such as hot dogs, chocolate, cheese and ice cream - the list is endless - could help alleviate symptoms. A trigger may occur up to 24 hours prior to the onset of symptoms. The majority of migraines are not however caused by identifiable triggers.

Management

There are three main aspects of treatment: trigger avoidance, acute symptomatic control, and pharmacological prevention. Medications are more effective if used earlier in an attack.

Analgesics

A number of analgesics are effective for treating migraines including:

- Non-steroidal anti-inflammatory drugs (NSAIDs): Ibuprofen provides pain effective pain relief in about half of people. Naproxen can abort about one third of migraine attacks, which was 5% less than the benefit of sumatriptan. A 1000 mg dose of Aspirin (also called ASA) could relieve moderate to severe migraine pain, with similar effectiveness to sumatriptan.
- Paracetamol/acetaminophen either alone or in combination with metaclopramide is effective for migraines.
- Simple analgesics combined with caffeine may help. During a migraine attack, emptying of the stomach is slowed, resulting in nausea and a delay in absorbing medication. Caffeine has been shown to partially reverse this effect. Excedrin is an example of an aspirin with caffeine product. Caffeine is recognized by the U.S. Food and Drug Administration as an Over The Counter Drug (OTC) treatment for migraine when compounded with aspirin and paracetamol. Even by itself, caffeine can be helpful during an attack, despite the fact that in general migraine-sufferers are advised to limit their caffeine intake.

CAUTION The frequent use of analgesics often results in a condition known as Medication Overuse Headache (MOH), in which the headaches gradually become more severe and more frequent, so caution should be exercised. MOH is known to occur with frequent use of many different medications including most commonly: triptans, ergotamines, analgesics, especially when mixed with caffeine and codeine, and opioids.

Triptans

Triptans such as sumatriptan are effective for both pain and nausea in up to 75% of people. They come in a number of different forms including oral, injection, nasal spray, and oral dissolving tablets. Most side effects are mild such as flushing however rare cases of myocardial ischemia have occurred. They are non addictive, but are potent causes of medication overuse headaches (MOH) if used more than 10 days per month.

Ergotamines

Dihydroergotamine is an older medication that some find useful. They were the primary oral drugs available to abort a migraine prior to the triptans. They are much less expensive than triptans. Ergotamine continues to be prescribed for migraines.

CAUTION The frequent use of ergotamines is a potent cause of a condition known as Medication Overuse Headache (MOH), in which the headaches gradually become more severe and more frequent, so caution should be exercised. MOH is known to occur with frequent use of many different medications including most commonly: triptans, ergotamines, analgesics, especially when mixed with caffeine and codeine, and opioids.

Steroids

A single dose of intravenous dexamethasone, when added to standard treatment of a migraine attack, is associated with a 26% decrease in headache recurrence in the following 72 hours.

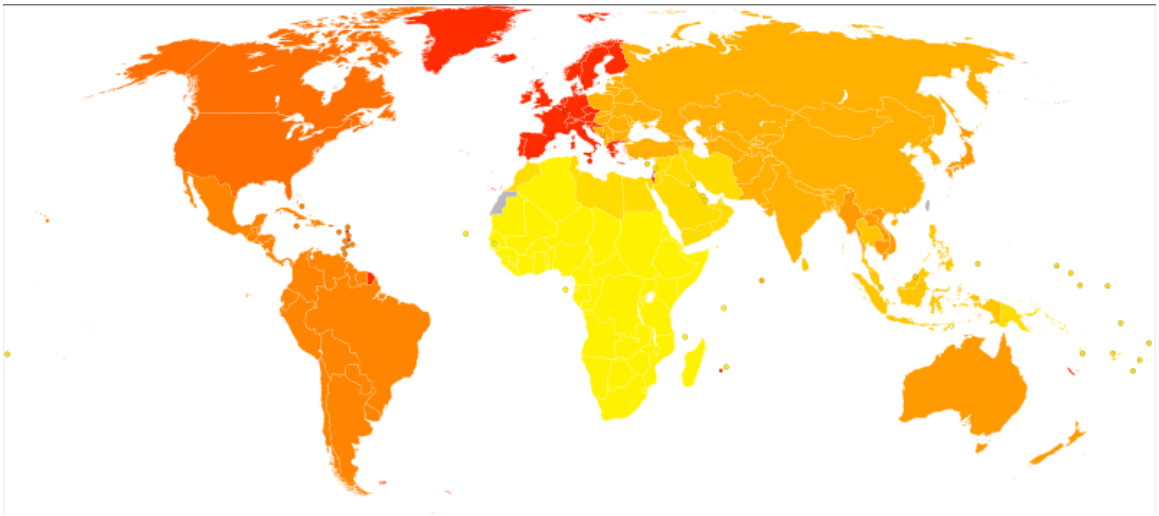
Other

Antiemetics by mouth may help relieve symptoms of nausea and help prevent vomiting, which can diminish the effectiveness of orally taken analgesia. In addition some antiemetics such as metoclopramide are prokinetics and help gastric emptying which is often impaired during episodes of migraine. In the UK, there are three combination antiemetic and analgesic preparations available: MigraMax (aspirin with metoclopramide), Migraleve (paracetamol/codeine for analgesia, with buclizine as the antiemetic) and paracetamol/metoclopramide (Paramax in UK). The earlier these drugs are taken in the attack, the better their effect.

Prognosis

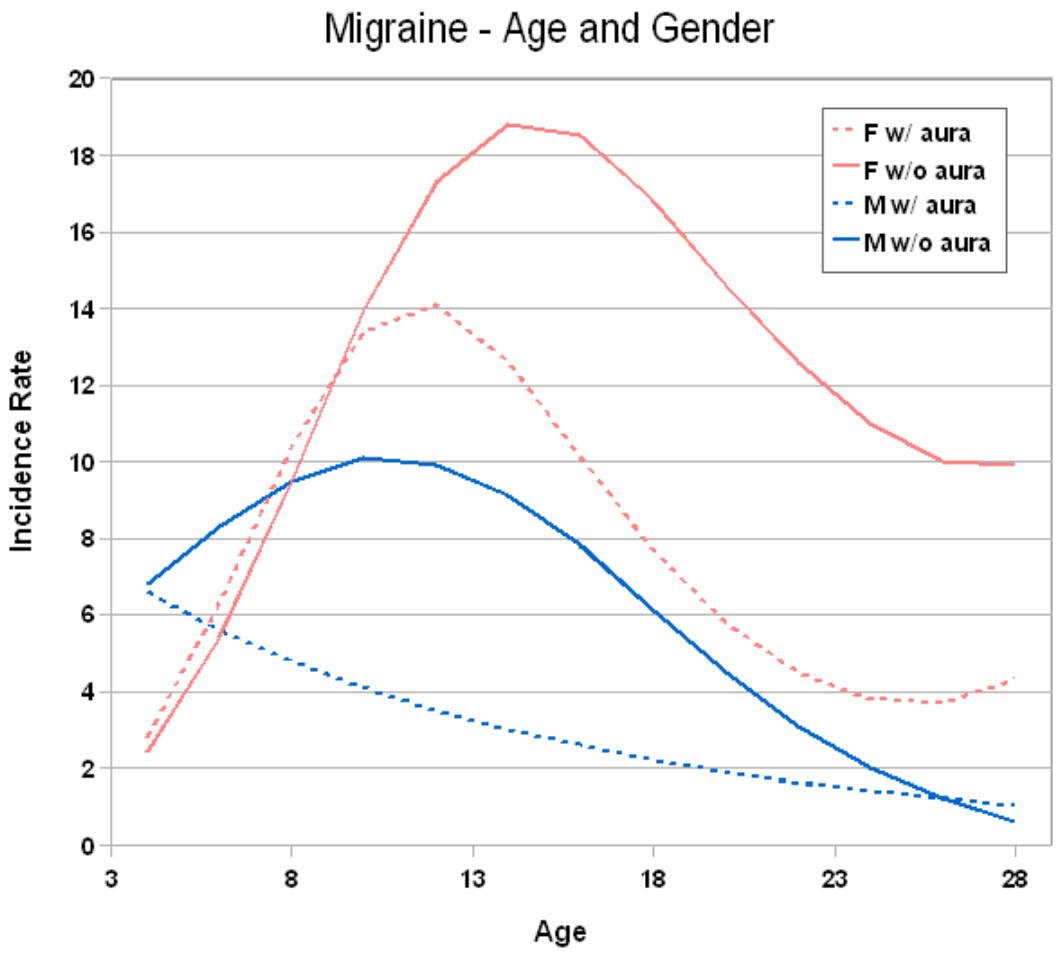
The risk of stroke may be increased two- to threefold in migraine sufferers. Young adult sufferers and women using hormonal contraception appear to be at particular risk. The mechanism of any association is unclear, but chronic abnormalities of cerebral blood vessel tone may be involved. Women who experience auras have been found to have twice the risk of strokes and heart attacks over non-aura migraine sufferers and women who do not have migraines. (Note: Women who experience auras and also take oral contraceptives have an even higher risk of stroke). Migraine sufferers seem to be at risk for both thrombotic and hemorrhagic stroke as well as transient ischemic attacks. Death from cardiovascular causes was higher in people with migraine with aura in a Women's Health Initiative study, but more research is needed to confirm this.

Epidemiology



Disability-adjusted life year for migraines per 100,000 inhabitants in 2002.

- no data
- less than 45
- 45-65
- 65-85
- 85-105
- 105-125
- 125-145
- 145-165
- 165-185
- 185-205
- 205-225
- 225-245
- more than 245



Age-Gender Incidence

Worldwide migraines affect more than 10% of people. In the United States approximately 6% of men and 18% of women get a migraine in a given year with a lifetime risk of about 18% and 43% respectively. In Europe migraines affect 12–28% of people at some point in their lives. Based on the results of a number of studies, one year prevalence of migraine ranges from 6–15% in adult men and from 14–35% in adult women. These figures vary substantially with age: approximately 4–5% of children aged under 12 suffer from migraine, with little apparent difference between boys and girls. There is then a rapid growth in incidence amongst girls occurring after puberty, which continues throughout early adult life. By early middle age, around 25% of women experience a migraine at least once a year, compared with fewer than 10% of men. After menopause, attacks in women tend to decline dramatically, so that in the over 70s there are approximately equal numbers of male and female sufferers, with prevalence returning to around 5%.

At all ages, migraine without aura is more common than migraine with aura, with a ratio of between 1.5:1 and 2:1. Incidence figures show that the excess of migraine seen in

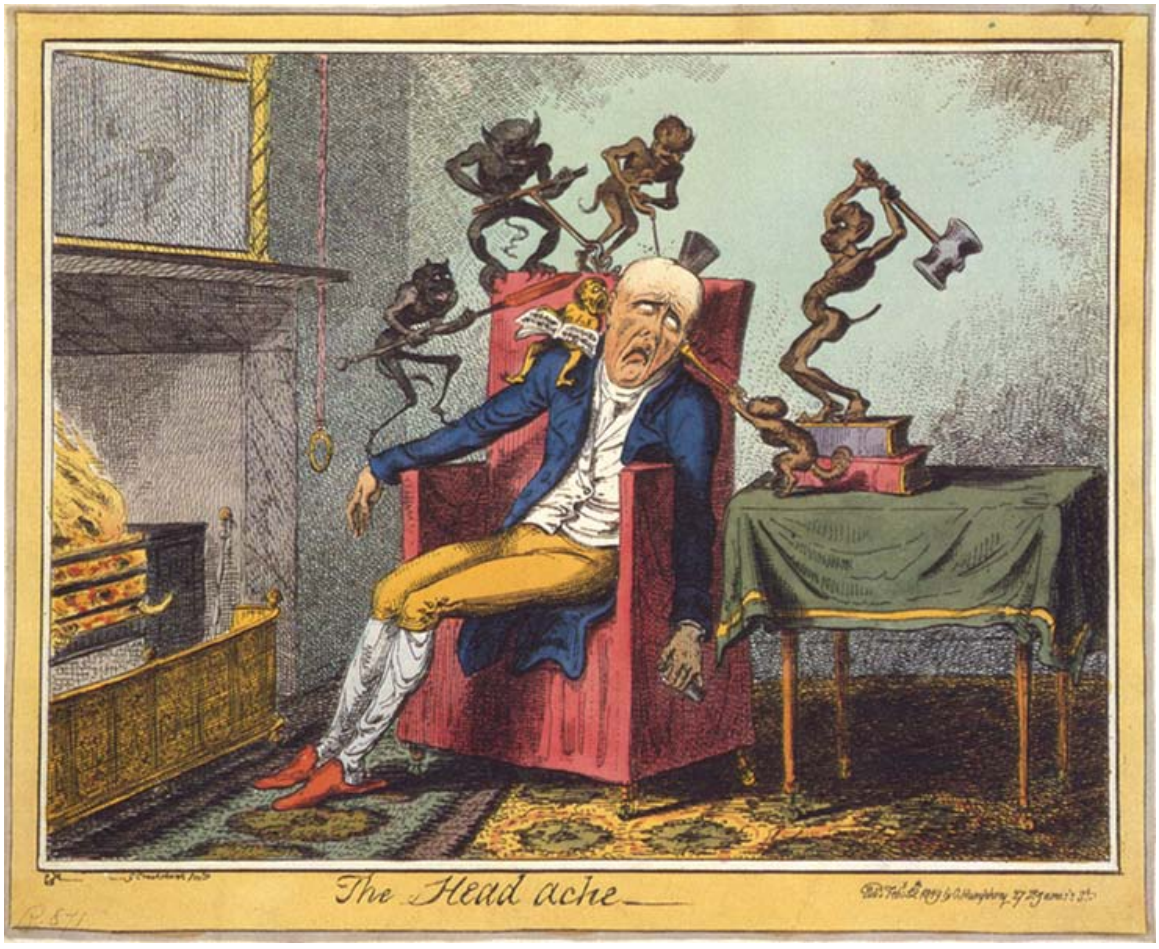
women of reproductive age is mainly due to migraine without aura. Thus in pre-pubertal and post-menopausal populations, migraine with aura is somewhat more common than amongst 15–50 year olds.

There is a strong relationship between age, gender and type of migraine.

Studies in Asia and South America suggest that the rates there are relatively low, but they do not fall outside the range of values seen in European and North American studies.

The incidence of migraine is related to the incidence of epilepsy in families, with migraine twice as prevalent in family members of epilepsy sufferers, and more common in epilepsy sufferers themselves.

History



The Head Ache. George Cruikshank (1819)

Trepanation, the deliberate and (usually) non-fatal drilling of holes into a skull, was practiced 9,000 years ago and earlier. Some scholars have (controversially) speculated that this drastic procedure might have been a migraine treatment, based on cave paintings and on the fact that trepanation *was* a historical migraine treatment in 17th-century

Europe. An early written description consistent with migraines is contained in the Ebers papyrus, written around 1200 BC in ancient Egypt.

In 400 BC Hippocrates described the visual aura that can precede the migraine headache and the relief which can occur through vomiting. Aretaeus of Cappadocia is credited as the "discoverer" of migraines because of his second century description of the symptoms of a unilateral headache associated with vomiting, with headache-free intervals in between attacks.

Galenus of Pergamon used the term "hemicrania" (half-head), from which the word "migraine" was derived. He thought there was a connection between the stomach and the brain because of the nausea and vomiting that often accompany an attack. For relief of migraine, Andalusian-born physician Abulcasis, also known as Abu El Qasim, suggested application of a hot iron to the head or insertion of garlic into an incision made in the temple.

In the Middle Ages migraine was recognized as a discrete medical disorder with treatment ranging from hot irons to bloodletting and even witchcraft. Followers of Galenus explained migraine as caused by aggressive yellow bile. Ebn Sina (Avicenna) described migraine in his textbook "El Qanoon fel teb" as "... small movements, drinking and eating, and sounds provoke the pain... the patient cannot tolerate the sound of speaking and light. He would like to rest in darkness alone." Abu Bakr Mohamed Ibn Zakariya Râzi noted the association of headache with different events in the lives of women, "...And such a headache may be observed after delivery and abortion or during menopause and dysmenorrhea."

In *Bibliotheca Anatomica, Medic, Chirurgica*, published in London in 1712, five major types of headaches are described, including the "Megrim", recognizable as classic migraine. The term "Classic migraine" is no longer used, and has been replaced by the term "Migraine with aura" Graham and Wolff (1938) published their paper advocating ergotamine tartrate for relieving migraine. Later in the 20th century, Harold Wolff (1950) developed the experimental approach to the study of headache and elaborated the vascular theory of migraine, which has come under attack as the pendulum again swings to the neurogenic theory. Recently however, there has been renewed interest in Wolff's vascular theory of migraine led by Elliot Shevel, a South African headache specialist, who has published a number of articles providing compelling evidence that Wolff was in fact correct.

Society and culture

Economic impact

Chronic migraine attacks are a significant source of both medical costs and lost productivity. It has been estimated to be the most costly neurological disorder in the European Community, costing more than €27 billion per year. Medical costs per migraine sufferer (mostly physician and emergency room visits) averaged $107 USD over six

months in one 1988 study, with total costs including lost productivity averaging $313. Annual employer cost of lost productivity due to migraines was estimated at $3,309 per sufferer. Total medical costs associated with migraines in the United States amounted to one billion dollars in 1994, in addition to lost productivity estimated at thirteen to seventeen billion dollars per year. Employers may benefit from educating themselves on the effects of migraines in order to facilitate a better understanding in the workplace. The workplace model of 9–5, 5 days a week may not be viable for a migraine sufferer. With education and understanding an employer could compromise with an employee to create a workable solution for both.

Research

Merck Corp is developing a new drug called Telcagepant which is intended to relieve pain without causing vasoconstriction (narrowing of blood vessels) as current medications such as triptans do. Telcagepant would be a safe therapy for migraine suffers with risk factors for cardiovascular disease.

Recently it has been found that calcitonin gene related peptides (CGRPs) play a role in the pathogenesis of the pain associated with migraine as triptans also decrease its release and action. CGRP receptor antagonists such as olcegepant and telcagepant are being investigated both in vitro and in clinical studies for the treatment of migraine.

In 2010, scientists identified a genetic defect linked to migraines which could provide a target for new drug treatments.

Chapter 2

ICHD Classification and Diagnosis of Migraine

The classification of all headaches, including migraines, is organized by the International Headache Society, and published in the International Classification of Headache Disorders (ICHD). The current version, the ICHD-2, was published in 2004.

The first category within the ICHD is *Migraine*. Migraines in general are considered to be a neurological syndrome. It is estimated that 11% (303 million) of the global population, including 43 million Europeans and 28 million Americans, experience migraines.

Organization of migraine subclasses

The ICHD-2 categorization includes 6 subclasses of migraine (formerly 7), most of which are further subdivided. The following table outlines these classes and their ICHD-1, -2, and ICD-10 codes.

ICHD-2	ICHD-1	ICD-10	ICHD-2 Diagnosis
1.1	1.1	G43.0	Migraine without aura
1.2	1.2	G43.1	Migraine with aura
1.3	1.5	G43.82	Childhood periodic syndromes that are commonly precursors of migraine
1.4	1.4	G43.81	Retinal migraine
1.5	1.6	G43.3	Complications of migraine
1.6	n/a	G43.3 (G40.; G41.)	Migraine-triggered seizure
1.7	n/a	G43.83	Probable migraine
n/a	1.3		Opthalmoplegic migraine
n/a	1.7		Migrainous disorder not fulfilling above criteria

Migraine without aura (common migraine)

Diagnostic criteria for *migraine without aura*:
A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours [*when untreated in adults*]
C. Headache has at least two of the following characteristics:

1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity

D. During the headache, at least one of the following [is present]:

1. Nausea and/or vomiting
2. Photophobia and phonophobia

E. Not attributable to another disorder

International Headache Society

Often referred to as a *common migraine*, *migraine without aura* (previously known as *hemicrania simplex*) is a specific neurological disorder characterized by recurrent, throbbing headaches that often affect one side of the head (i.e., it is unilateral), are of at least moderate intensity, and may cause nausea, phonophobia or photophobia. One defining characteristic of the common migraine is a lack of the visual disturbances known as an aura. The exact International Classification of Headache Disorders diagnostic criteria appear to the right.

Because migraine without aura can be hard to distinguish from an *infrequent episodic tension-type headache*, 5 attacks must have been experienced to meet the diagnosis. When migraine with aura is likely, but 5 attacks have not occurred, a diagnosis of *probable migraine without aura* (ICHD-2: 1.6.1) is warranted.

For children, the criteria are slightly less strict. For a pediatric diagnosis of migraine without aura, each attack need only last 1 hour to qualify. Also, pediatric migraines are frequently bilateral (on both sides of the head); unilaterality is not the typical pattern for migraineurs until late adolescence.

Note also that migraine without aura can be diagnosed even if a patient has before experienced an aura.

One popular theory in migraine pathophysiology is the depolarization theory, which centres around the phenomenon of cortical spreading depression. However, it appears that this theory can not account for migraine without aura. Blood flow imaging has revealed no evidence of this phenomenon, though it has noted some changes in blood flow that are secondary to pain activation, particularly in the brainstem.

Research has revealed that nitric oxide (NO) and calcitonin gene-related peptide (CGRP) do have roles in the pathogenesis of a migraine without aura attack. Several studies have shown that migraines without aura develop in most subjects after the infusion of glyceryl trinitrate (GTN, well known as nitroglycerin), which is known to transport NO to tissues, but only in patients who are migraine sufferers. As well, inhibition of the nitric oxide synthase enzymes (NOS) by L-nitromonomethylarginine (L-NMMA) successfully reduced pain severity (in contrast with a placebo) in spontaneous attacks of migraine without aura.

In general, migraine without aura is more common than migraine with aura, with more frequent and more disabling attacks.

Menstrual migraines

Diagnostic criteria for *Pure menstrual migraine without aura* (A1.1.1)
A. Attacks, in a menstruating woman, fulfilling the criteria for *migraine without aura*
B. Attacks that occur exclusively from days -2 to +3 of menstruation in at least 2 out of 3 menstrual cycles and at no other times of the cycle.

Note: The first day of menstruation is day +1, and the preceding day is day -1; there is no day 0.

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Diagnostic criteria for *Menstrually-related migraine without aura* (A1.1.2)
A. Attacks, in a menstruating woman, fulfilling the criteria for *migraine without aura*
B. Attacks that occur exclusively from days -2 to +3 of menstruation in at least 2 out of 3 menstrual cycles, and additionally at other times of the menstrual cycle.

Note: The first day of menstruation is day +1, and the preceding day is day -1; there is no day 0.

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It is well documented that migraine occurs nearly 3 times as often in women than in men, and is one of the top 5 most common disabling conditions in women. In over half these women, their headaches are strictly related to their menstrual cycle.

A clinical epidemiological study of women with migraine without aura in Parma and Pavia, Italy, revealed that 60% of those women experienced their attacks almost exclusively while menstruating, that 10.7% of their migraines first began at menarche (their very first "period", at puberty), and that 67% of them no longer had migraines while pregnant (and thus not menstruating).

This relationship was noted by the IHS in both versions of the ICHD, and particularly that this disorder fell under "migraine without aura". The ICHD-1 referred to this as *menstrual migraine*, noting that there were no strict guidelines for this diagnosis, but that at least 90% of a woman's attacks should occur within 2 days of the beginning or end of menstruation. When the ICHD-2 was published, explicit guidelines for a diagnosis of 2 distinct types of menstruation-related migraine were released, and appear to the right.

However, because the nature of the relationship is still unclear, and because the IHS was still uncertain as to whether these were a subset of migraine without aura or a distinct class of migraine, the criteria were delegated to an appendix, while anticipating that they would appear within the main text in the next revision.

The ICHD-2 specifies 2 different forms of the previously-dubbed "menstrual migraine": *pure menstrual migraine without aura* and *menstrually-related migraine without aura*. The sole difference between these diagnoses is the occurrence of headache attacks outside of the 5-day period described in the diagnostic criteria. If a woman experiences no attacks outside of this 5-day period, she may be diagnosed with pure menstrual migraine with aura; if she does experience other attacks, however, she may suffer from menstrually-related migraine without aura. This distinction is made solely for treatment purposes; a woman who only experiences migraines in that 5-day period is likely to benefit more from hormone therapy than a traditional migraine medication such as a triptan.

One defining characteristic of these menstrual migraines is that the woman does not experience an aura. Clinical research has shown migraine with aura to be unrelated to the menstrual cycle, and, in women who have headaches sometimes with aura and sometimes without, the presence or absence of aura does not appear to be related to the menstrual cycle.

As well as being split into 2 classes, menstrual migraines may have 2 different pathophysiologies, based on whether or not a woman is taking any oral contraceptives or another form of cyclical hormone replacement therapy. When these medications are being used, the regular hormonal changes that take place and result in ovulation and other events in the menstrual cycle are suppressed, and menstruation is instead the result of withdrawal from abnormal progestogen concentrations.

Menstrual migraines may also be linked to oestrogen withdrawal. Under the category of *headache attributed to a substance or its withdrawal*, the ICHD specifies the diagnostic criteria for *oestrogen-withdrawal headache* (8.4.3, G44.83 and Y42.4), and suggests that both that diagnosis and one of the menstrual migraine diagnoses be used in case of migraines related to oestrogen withdrawal occurring mainly at menstruation.

Migraine with aura

The second-most common form of migraine headache: the patient primarily suffers migraine with aura, and might also suffer migraine without aura. The International Classification of Headache Disorders definition is:

Description: Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5–20 minutes and last for less than 60 minutes. Headache with the features of "migraine without aura" usually follows the aura symptoms. Less commonly, headache lacks migrainous feature or is completely absent [i.e., the aura may occur without any subsequent headache].

Diagnostic criteria:
A. At least two attacks fulfilling criterion B
B. Migraine aura fulfilling criteria [described below]
C. Not attributed to another disorder.

...[**Criteria for "Typical aura"**:]
Aura consisting of at least one of the following, but no motor weakness:
1. Fully reversible visual symptoms including positive features (e.g. flickering lights, spots or lines) and/or negative features (i.e., loss of vision)
2. Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness)
3. Fully reversible dysphasic speech disturbance
[Aura also has] at least two of the following:
1. Homonymous visual symptoms [i.e., affecting just one side of the field of vision] and/or unilateral sensory symptoms [i.e., affecting just one side of the body]
2. At least one aura symptom develops gradually over [at least] 5 minutes and/or different aura symptoms occur [one after the other] over [at least] 5 minutes
3. Each symptom lasts [from] 5 [to] 60 minutes

...[**Other potential aura criteria**:]

- Fully reversible motor weakness...
- Each aura symptom lasts [from] 5 minutes [to] 24 hours...
- [In the case of a "Basilar-type" migraine], Dysarthria [difficulty speaking], vertigo [dizziness], tinnitus [ringing in the ears], [and other symptoms].

– International Classification of Headache Disorders

Basilar type migraine

Basilar type migraine (BTM) (previously basilar artery migraine [BAM] and basilar migraine [BM]) is an uncommon, complicated migraine with symptoms caused by brainstem dysfunction. Serious episodes of BTM can lead to stroke, coma, and death. Using triptans and other vasoconstrictors as abortive treatments for BTM is contraindicated. Abortive treatments for BTM address vasodilation and restoration of normal blood flow to the vertebrobasilar territory to restore normal brainstem function.

Familial and sporadic hemiplegic migraine

Familial hemiplegic migraine (FHM) is migraine with a possible polygenetic cause—in fact, FHM can only be diagnosed when at least one close relative has it too. The patient experiences typical migraine with aura headache either preceded or accompanied with one-sided, reversible limb weakness and/or sensory difficulties and/or speech difficulties. FHM is associated with ion channel mutations.

There also exists the "sporadic hemiplegic migraine" (SHM), which is the same as FHM but with no close family members showing the symptoms.

Effecting a differential diagnosis between basilar migraine and hemiplegic migraine is difficult. Often, the decisive symptom is either motor weakness or unilateral paralysis, which occur in FHM and SHM. Basilar migraine can present tingling and numbness, but true motor weakness and paralysis occur only in hemiplegic migraine.

Abdominal migraine

Abdominal migraine is a recurrent disorder of unknown origin, principally affecting children. Sometimes early on, it can be misdiagnosed in an ER setting as appendicitis. Episodes feature nausea, vomiting, and moderate-to-severe central, abdominal pain. The child is well between episodes. The International Classification of Headache Disorders definition is:

Diagnostic criteria:

> A. At least 5 attacks fulfilling criteria B-D.
> B. Attacks of abdominal pain lasting 1-72 hours (untreated or unsuccessfully treated)
> C. Abdominal pain has all of the following characteristics:
> 1. midline location, periumbilical or poorly localized
> 2. dull or "just sore" quality
> 3. moderate or severe intensity
> D. During abdominal pain at least 2 of the following:
> 1. anorexia
> 2. nausea
> 3. vomiting
> 4. pallor
> E. Not attributed to another disorder
>
> *– International Classification of Headache Disorders*

Most children suffering abdominal migraine will develop propensity to migraine headache in adult life; the two propensities might co-exist during the child's adolescence.

Treating an abdominal migraine can often be difficult; medications used to treat other forms of migraines are usually employed. These include Elavil (75-150 mg), Wellbutrin SR (400 mg), and Topamax (200-400 mg).

In some cases, the abdominal migraine is a symptom linked to cyclic vomiting syndrome (CVS). There may be a history of migraines in the family of the sufferer.

Retinal migraine

Retinal migraines are a subclass of optical migraines. Sufferers will experience a scotoma—a patch of vision loss in one eye surrounded by normal vision—for less than one hour before vision returns to normal. Retinal migraines may be accompanied by a throbbing unilateral headache, nausea, or photophobia.

Not classified in the ICHD-2 under migraine

Acephalgic migraine

Acephalic migraine is a neurological syndrome. It is a variant of migraine in which the patient may experience aura symptoms such as scintillating scotoma, nausea, photophobia, hemiparesis and other migraine symptoms but does not experience headache. Acephalic migraine is also referred to as **amigrainous migraine**, **ocular migraine**, **ophthalmic migraine** or **optical migraine**.

Sufferers of acephalgic migraine are more likely than the general population to develop classical migraine with headache.

The prevention and treatment of acephalgic migraine is broadly the same as for classical migraine. However, because of the absence of "headache", diagnosis of acephalic migraine is apt to be significantly delayed and the risk of misdiagnosis significantly increased.

Visual snow might be a form of acephalic migraine.

If symptoms are primarily visual, it may be necessary to consult an ophthalmologist or optometrist to rule out potential eye disease before considering this diagnosis.

Chapter 3

Familial Hemiplegic Migraine

Familial hemiplegic migraine	
ICD-10	G43.1
ICD-9	346.8
OMIM	141500 602481 609634 607516
DiseasesDB	4693
eMedicine	neuro/219

Familial hemiplegic migraine (FHM) is an autosomal dominant classical migraine subtype that typically includes hemiparesis (weakness of half the body) during the aura phase. It can be accompanied by other symptoms, such as ataxia, coma and epileptic seizures. There is clinical overlap in some FHM patients with episodic ataxia type 2 and spinocerebellar ataxia type 6, benign familial infantile convulsions, and alternating hemiplegia of childhood. There are 3 known loci for FHM. FHM1, which accounts for approximately 50% of FHM patients, is caused by mutations in a gene coding for the P/Q-type calcium channel α subunit, CACNA1A. FHM1 is also associated with cerebellar degeneration. FHM2, which accounts for <25% of FHM cases, is caused by mutations in the Na^+/K^+-ATPase gene ATP1A2. FHM3 is a rare subtype of FHM and is caused by mutations in a sodium channel α-subunit coding gene, SCNA1. These three subtypes do not account for all cases of FHM, suggesting the existence of at least one other locus (FHM4). Many of the non-familial cases of hemiplegic migraine (sporadic hemiplegic migraine) are also caused by mutations at these loci.

Classification

FHM can be loosely divided into two categories: with and without cerebellar signs. Cerebellar signs refer to ataxia, sometimes episodic and other times progressive, that can accompany FHM1 mutations and is caused by degeneration of the cerebellum. These cerebellar signs result in a phenotypic overlap between FHM and both episodic ataxia and spinocerebellar ataxia. This is unsurprising as subtypes of these disorders (FHM1,

EA2 and SCA6) are allelic, i.e., they result from mutations in the same gene. The other forms of FHM seem to be distinguishable only on the basis of their genetic cause.

There are also non-familial cases of hemiplegic migraine, termed sporadic hemiplegic migraine. These cases seem to have the same causes as the familial cases and represent de novo mutations. Sporadic cases are also clinically identical to familial cases with the exception of a lack of family history of attacks.

Signs and symptoms

FHM signs overlap significantly with those of migraine with aura. In short, FHM is typified by migraine with aura associated with hemiparesis and, in FHM1, cerebellar degeneration. This cerebellar degeneration can result in episodic or progressive ataxia. FHM can also present with the same signs as benign familial infantile convulsions (BFIC) and alternating hemiplegia of childhood. Other symptoms are altered consciousness (in fact, some cases seem related to head trauma), gaze-evoked nystagmus and coma. Aura symptoms, such as numbness and blurring of vision, typically persist for 30–60 minutes. These signs typically first manifest themselves in the first or second decade of life.

Causes

It is believed that FHM mutations lead to migraine susceptibility by lowering the threshold for cortical-spreading-depression generation. The FHM1 and FHM3 mutations are occur in ion channels expressed in neurons. These mutations may lead to both the hyper and hypoexcitable neurons that might underlie cortical-spreading-depression. It is even less clear how the mutations seen in FHM2 patients might lead to FHM symptoms as the gene mutated in FHM2 is expressed primarily in astrocytes. One proposal states that the depolarization of astrocytes caused by haploinsufficiency of the ATP1A2 Na+/K+-ATPase causes increased release of compounds such as adenosine from astrocytes. These compounds then interact with neighboring neurons, altering their excitability and leading to cortical-spreading-depression and migraine.

Diagnosis

Diagnosis of FHM is made according to the following criteria:

- Two attacks of each of the following:
    - Aura with motor weakness accompanied by either reversible visual symptoms (flickering lights, spots, lines, etc.), reversible sensory symptoms (pins and needles, numbness, etc.) or speech symptoms.
    - At least two occurrences of:
    - One or more aura symptoms that develop over at least 5 minutes
    - These symptoms lasting more than 5 minutes and less than 24 hours

- Headache beginning within 60 minutes of aura onset. These headaches can last 4-72 hours, occur on only one side of the head, pulsate, be of moderate to severe intensity, and may be aggravated by common physical activities such as walking. These headaches must also be accompanied by nausea/vomiting, phonophobia (avoidance of sound due to hypersensitivity) and/or photophobia (avoidance of light due to hypersensitivity).

- At least one close (first or second degree) relative with FHM
- No other likely cause

Sporadic forms follow the same diagnostic criteria, with the exception of family history.

In all cases, family and patient history is used for diagnosis. EEG and brain imaging techniques, such as MRI and CAT scans, are used to rule out epilepsy and to test for cerebellar degeneration, respectively. With the discovery of causative genes, genetic sequencing can also be used to verify diagnosis (though not all genetic loci are known).

Pathophysiology

FHM1 (CACNA1A)

The first discovered FHM locus was the CACNA1A gene (originally named CACNL1A4), which encodes the P/Q-type calcium channel $Ca_V2.1$. There are currently 17 known mutations in this channel, see Table 1, and these mutations are distributed throughout the channel. Some of these mutations result in patients with notable cerebellar degeneration or other dysfunction. 15 of these mutants have received at least some further analysis at the electrophysiological level to attempt to determine how they might lead to the FHM1 phenotype. There is increasing contradiction in the literature as to the end result of these mutations on channel kinetics and neuronal excitability.

A good example of this contradiction can be seen in the literature regarding the R192Q mutation. The first investigation of this mutation, using the rabbit isoform of the channel expressed in oocytes, found that it did not alter any measured channel properties. A subsequent report, using human channels expressed in HEK293 Cells, found a small hyperpolarizing shift in the midpoint for activation, a result common among FHM1 mutants. This shift results in channels that open at more negative potentials and, thus, have a higher open probability than wild-type channels at most potentials. This report also found that the R192Q mutant produced almost twice as much whole-cell current compared to wild-type channels. This is not due to a change in single channel conductance but to an equivalent increase in channel density. A subsequent group noticed that this mutation is in a region important for modulation by G protein-coupled receptors (GPCRs). GPCR activation leads to inhibition of wild-type $Ca_V2.1$ currents. R192Q mutant channel currents are also decreased by GPCR activation, but by a smaller amount. A more recent group has confirmed some of these results by creating a R192Q knock-in mouse. They confirmed that the R192Q mutant activates at more negative potentials and

that neurons producing these channels have much larger whole-cell current. This resulted in a much larger quantal content (the number of neurotransmitter packets released per action potential) and generally enhanced neurotransmitter release in R192Q expressing neurons versus wild-type. Consequently, these mutant mice were more susceptible to cortical-spreading-depression than their wild-type counterparts. The most recent experiments on this mutant, however, have contradicted some of these results. In $Ca_V2.1$ knockout neurons transfected with human channels, P/Q-type currents from mutant channels are actually smaller than their wild-type counterpart. They also found a significant decrease in calcium influx during depolarization, leading to decreased quantal content, in mutant versus wild-type expressing neurons. Neurons expressing mutant channels were also less able to mediate inhibitory input and have smaller inhibitory postsynaptic currents through P/Q-type channels. Further testing with this and other mutants is required to determine their end affect on human physiology.

Table 1. Summary of mutations in CACNA1A found in patients diagnosed with FHM type 1

Mutation					
Nucleotide	**Amino acid**	**Position**	**Effect**	**Cerebellar signs**	**Reference**
c.G575A	**R192Q**	D1S4	Increases G-protein mediated inhibition, activates at more negative potentials, increased expression, faster recovery from inactivation. In mice: greater current, activates at more negative potentials, enhances transmitter release	?	,,,,,
c.G584A	**R195K**	D1S4		No	
c.C653T	**S218L**	D1S4-5	Increases sojourns to subconductances, activates at more negative potentials, decreased slow inactivation, increased fast inactivation	Yes	,
c.G1748A	**R583Q***	D2S4	Activates at more negative potentials, faster current decay, faster inactivation, slower recovery from inactivation	Yes	,,,,
c.C1997T	**T666M**	D2-pore	Activates at more negative potentials, faster current decay, slowed recovery from inactivation, smaller single channel conductance, higher i*Po, slower recovery from inactivation, Increased G-protein mediated inhibition, decreased	Yes	,,,,,,,,

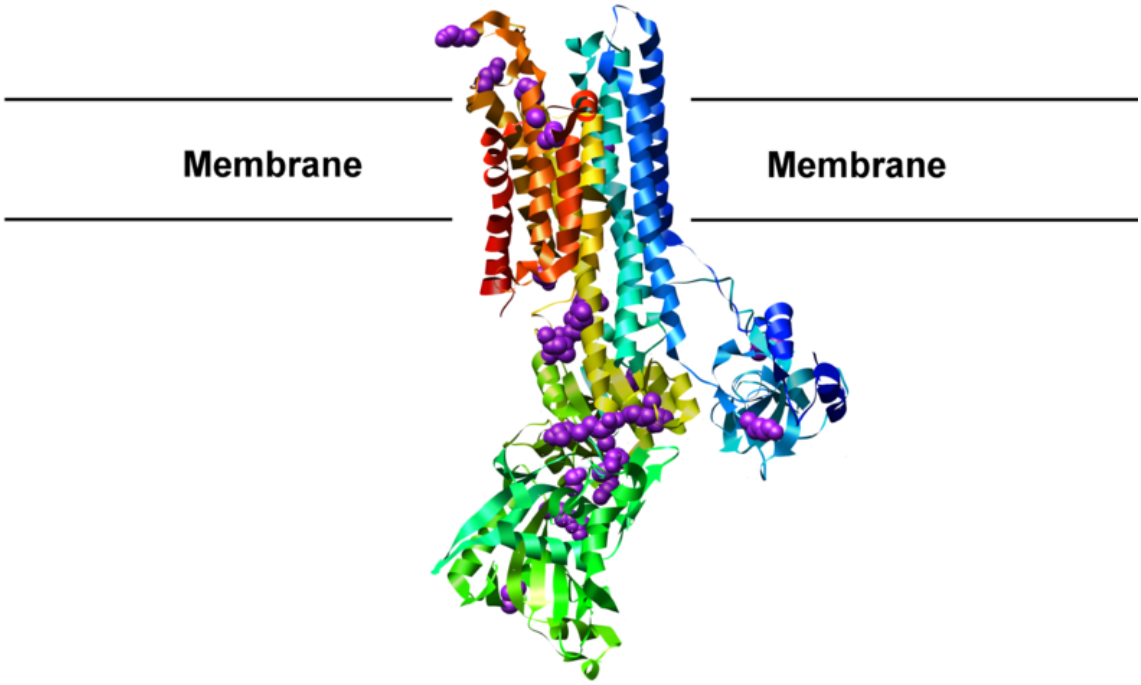
			gating charge (fewer channels available to open)		
c.T2141C	**V714A**	D2S6	Activates at more negative potentials, faster current decay, faster recovery from inactivation, decreases expression, faster recovery from inactivation, increases G-protein mediated inhibition	No	””
c.C2145G	**D715E**	D2S6	Activates at more negative potentials, faster current decay, faster inactivation	Yes	”
c.A4003G	**K1335E**	D3S3-4	Activates at more negative potentials, inactivates at more negative potentials, slowed recovery from inactivation, increased frequency dependent rundown	No	’
c.G4037A	**R1346Q**	D3S4		Yes	
c.A4151G	**Y1384C**	D3S5		Yes	’
c.G4366T	**V1456L**	D3-pore	Activates at more negative potentials, slower current decay, slower recovery from inactivation	No	’
c.C4636T	**R1546X****	D4S1	Decreased current	Yes	”
c.C4999T	**R1667W**	D4S4		Yes	
c.T5047C	**W1683R**	D4S4-5	Activates at more negative potentials, inactivates at more negative potentials, slowed recovery from inactivation, increased frequency dependent rundown	Yes	’
c.G5083A	**V1695I**	D4S5	Slowed recovery from inactivation, increased frequency dependent rundown	No	’
c.T5126C	**I1709T**	D4S5		Yes	’
c.A5428C	**I1810L**	D4S6	Activates at more negative potentials, faster recovery from inactivation, decreased expression, faster recovery from inactivation, Increased G-protein mediated inhibition	Yes	””

* Also diagnosed as spinocerebellar ataxia type-6

** Also diagnosed as episodic ataxia type-2

Sequence numbering according to NCBI reference sequence NM_000068.2. Cerebellar signs refers to findings of cerebellar degeneration or ataxia upon clinical examination.

FHM2 (ATP1A2)



The crystal structure of the Na^+/K^+-ATPase with FHM2 mutations noted in purple. The N-terminus is colored blue and the C-terminus red. The approximate location of the cell membrane is noted. The original pdb file is available here.

The second subtype of familial hemiplegic migraine, FHM2, is caused by mutations in the gene ATP1A2 that encodes a Na^+/K^+-ATPase. This Na^+/K^+-ATPase is heavily expressed in astrocytes and helps to set and maintain their reversal potential. There are 29 known mutations in this gene associated with FHM2, Table 2, many clustering in the large intracellular loop between membrane-spanning segments 4 and 5, Figure 1. 12 of these mutations have been studied by expression in model cells. All but one have shown either complete loss of function or more complex decreases in ATPase activity or potassium sensitivity. Astrocytes expressing these mutant ion pumps will have much higher resting potentials and are believed to lead to disease through a poorly understood mechanism.

Table 2. Summary of mutations in ATP1A2 found in patients diagnosed with FHM type 2

Mutation	Location	Physiological result	Reference(s)
E174K	M2-3	No change	
T263M	M2-3		
G301R	M3		
T345A	M4-5	Decreased K influx	’
T376M	M4-5		
R383H	M4-5		
T387N	M4-5		
C515Y	M4-5	Loss of function (haploinsufficiency)	
R548H	M4-5		
R593W	M4-5	Loss of function (haploinsufficiency)	
A606T	M4-5		
G615R	M4-5	Loss of function (haploinsufficiency)	
V628M	M4-5	Loss of function (haploinsufficiency)	
R689Q	M4-5	Decreased catalytic turnover	”
E700K	M4-5		
D718N	M4-5	Loss of function (haploinsufficiency)	
M731T	M4-5	Decreased catalytic turnover	”
R763H	M4-5	Loss of function (haploinsufficiency)	
L764P	M4-5	Loss of function (haploinsufficiency)	”
P796R	M5-6		
M829R	M6-7		
R834Q	M6-7		
W887R	M7-8	Loss of function (haploinsufficiency)	”’
E902K	M7-8		
935K_940SdelinsI	M8-9		
R937P	M8-9		
S966LfsX998	M9		
P979L	M9-10		
X1021RextX28	C-Terminus		

Numbering according to the NCBI reference sequence NM_000702.2.

FHM3 (SCN1A)

The final known locus for FHM is the SCN1A gene, which encodes a sodium channel α subunit. The only study so far that has found mutations in this gene discovered the same Q1489K mutation in 3 of 20 families (15%) with 11 other kindreds (55%) already having

mutations in CACNA1A or ATP1A2. This mutation is located in a highly conserved region of an intracellular loop connecting domains three and four. This mutation results in a greatly hastened (2-4 fold) recovery from inactivation compared to wild-type. As this channel is important for action potential generation in neurons, it is expected that the Q1489K mutant results in hyperexcitable neurons.

FHM4 (1q31)

The final known locus for FHM maps to the q-arm of chromosome 1. There are a number of attractive candidate genes in this area, though no mutations in them have yet been linked to FHM4.

Treatment/Management

Patients with FHM are encouraged to avoid activities that may trigger their attacks. Minor head trauma is a common attack precipitant, so FHM sufferers should avoid contact sports. Acetazolamide or standard drugs are often used to treat attacks, though those leading to vasoconstriction should be avoided due to the risk of stroke.

Prevention/Screening

Prenatal screening is not typically done for FHM, however it may be performed if requested. As penetrance is high, individuals found to carry mutations should be expected to develop signs of FHM at some point in life.

Epidemiology

Migraine itself is a very common disorder, occurring in 15-20% of the population. Hemiplegic migraine, be it familial or spontaneous, is less prevalent, 0.01% prevalence according to one report. Women are three times more likely to be affected than males.

Chapter 4

Retinal Migraine and Acephalgic Migraine

Retinal migraine

Retinal migraine	
ICD-10	G43.81

Retinal migraine (also known as **ophthalmic migraine** and **ocular migraine**) is a retinal disease often accompanied by migraine headache and typically affects only one eye. It is caused by a vascular spasm behind the affected eye.

Symptoms

Retinal migraine is associated with transient monocular visual loss (scotoma) in one eye lasting less than one hour. During some episodes, the visual loss may occur with no headache and at other times throbbing headache on the same side of the head as the visual loss may occur, accompanied by severe light sensitivity and/or nausea. After each episode, normal vision returns.

It may be difficult to read and dangerous to drive a vehicle while retinal migraine symptoms are present.

Retinal migraine is a different disease than scintillating scotoma, which is a visual anomaly caused by spreading depression in the occipital cortex, at the back of the brain, not in the eyes nor any component thereof, such as the retinas. Such a scintillating aura affects both eyes, and sufferers may see flashes of light; zigzagging patterns; blind spots; and shimmering spots or stars. In contrast, retinal migraine involves repeated bouts of temporary diminished vision or blindness in one eye.

Diagnosis

The medical exam should rule out any underlying causes, such as blood clot, stroke, or detached retina. A normal retina exam is consistent with retinal migraine.

Treatment

Treatment depends on identifying behavior that triggers migraine such as stress, sleep deprivation, skipped meals, food sensitivities, or specific activities. Medicines used to treat retinal migraines include aspirin, other NSAIDS, and medicines that reduce high blood pressure.

Prognosis

In general, the prognosis for retinal migraine is similar to that of migraine headache with typical aura. As the true incidence of retinal migraine is unknown, it is uncertain whether there is a higher incidence of permanent neuroretinal injury. The visual field data suggests that there is a higher incidence of end arteriolar distribution infarction and a higher incidence of permanent visual field defects in retinal migraine than in clinically manifest cerebral infarctions in migraine with aura. One study suggests that more than half of reported *recurrent* cases of retinal migraine subsequently experienced permanent visual loss in that eye from infarcts. An infarction in the retina, however, is usually apparent to the patient.

Acephalgic migraine

Acephalgic migraine (also called **acephalalgic migraine**, **migraine aura without headache**, **amigrainous migraine**, **isolated visual migraine** and **optical migraine**) is a neurological syndrome. It is a relatively uncommon variant of migraine in which the patient may experience aura, nausea, photophobia, hemiparesis and other migraine symptoms but does not experience headache. While it is generally classified as an event fulfilling the conditions of migraine with aura with no (or minimal) headache, it is sometimes distinguished from visual-only migraine aura without headache, also called ocular migraine.

Symptoms and misdiagnosis

Acephalgic migraines can occur in individuals of any age. Though there are some individuals—more commonly male—who only experience acephalgic migraine, frequently patients also experience migraine with headache. Generally, the condition is more than twice as likely to occur in females than males. Although not listed as such in the *International Classification of Headache Disorders*, pediatric acephalgic migraines

are listed along with other childhood periodic syndromes by W.A. Al-Twaijri and M.I. Shevell as "migraine equivalents", which can be good predictors of the future development of typical migraines. Individuals who experience acephalgic migraines only in childhood are highly likely to develop typical migraines as they grow older. Among women, incidents of acephalgic migraine increase during perimenopause.

Scintillating scotoma is the most common symptom. Also frequently reported is monocular blindness. Acephalgic migraines typically do not persist more than a few hours and may last for as little as 15 seconds. On rare occasions, they may continue for up to two days.

Acephalgic migraines may resemble transient ischemic attacks or, when longer in duration, stroke. The concurrence of other symptoms such as photophobia and nausea can help determining the proper diagnosis. Occasionally, patients with acephalgic migraine are misdiagnosed as suffering epilepsy with visual seizures, but the reverse misdiagnosis is more common.

Treatment

The prevention and treatment of acephalgic migraine is broadly the same as for classical migraine but, as the symptoms are usually less severe, treatment is less likely to be required.

Chapter 5

Aura (Symptom) and Cortical Spreading Depression

Aura (Symptom)

Migraine with aura (classical migraine)	
ICD-10	G43.1
ICD-9	346.0

Artist's depiction of zig-zag lines appearing as part of a migraine aura phenomenon

An **aura** is the perceptual disturbance experienced by some migraine sufferers before a migraine headache, and the telltale sensation experienced by some people with epilepsy

before a seizure. It often manifests as the perception of a strange light, an unpleasant smell or confusing thoughts or experiences. Some people experience aura without a subsequent migraine or seizure.

When occurring, auras allow epileptics time to prevent injury to themselves. The time between the appearance of the aura and the migraine lasts from a few seconds up to an hour. Most people who have auras have the same type of aura every time.

Auras can also be confused with sudden onset of panic, panic attacks or anxiety attacks creating difficulties in diagnosis. The differential diagnosis of patients who experience symptoms of paresthesias, derealization, dizziness, chest pain, tremors, and palpitations can be quite challenging.

Examples

An aura sensation can include some or a combination of the following:

Visual changes

- Bright lights and blobs
- Zigzag lines
- Distortions in the size or shape of objects
- Vibrating visual field
- Scintillating scotoma
    - Shimmering, pulsating patches, often curved
    - Tunnel vision
- Scotoma
    - Blind or dark spots in the field of vision
    - Curtain-like effect over one eye
    - Slowly spreading spots
- Kaleidoscope effects on visual field
- Total temporary monocular (in one eye) blindness (in retinal migraine)

Auditory changes

- Hearing voices or sounds that do not exist: true auditory hallucinations
- Modification of voices or sounds in the environment: buzzing, tremolo, amplitude modulation or other modulations

Other sensations

- Strange smells (Phantosmia)
- Gustatory Hallucinations
- Feelings of déjà vu or confusion
- Feelings of numbness or tingling on one side of the face or body
- Feeling separated from one's body

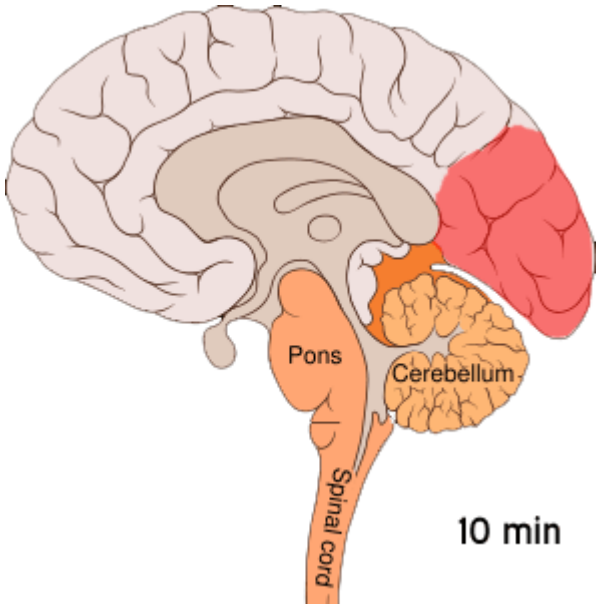
- Feeling as if the limbs are moving independently from the body
- Feeling as if one has to eat or go to the bathroom
- Anxiety or fear
- Weakness, unsteadiness
- Saliva collecting in the mouth
- Being unable to understand or comprehend spoken words during and after the aura
- Being unable to speak properly, such as slurred speech or gibberish, despite the brain grasping what the person is trying to verbalize (aphasia)

Uses

The specific type of sensation associated with an aura can potentially be used in an attempt to localize the focus of a seizure.

Auras share similar symptoms with strokes, but onset is more gradual with auras. Auras can last from several seconds to as long as an hour, and can sometimes end with feelings of extreme tiredness, weakness, heart palpitation, sweating and warmth throughout one's body.

Cortical spreading depression



Cortical spreading depression

Cortical spreading depression is a wave of electrophysiological hyperactivity followed by a wave of inhibition, usually in the visual cortex.

The term is used by neuroscientists to represent at least one of the following cortical processes:

- The spreading of a self-propagating wave of cellular depolarization in the cerebral cortex.
- The spreading of a wave of ischemia passing through an area of cortex.
- The spreading of a wave of vasoconstriction following vasodilation of contiguous cortical arterioles.

The scintillating scotoma of migraine in humans may be related to the neurophysiologic phenomenon termed the spreading depression of Leão.

The spreading depression wave progresses across the cortex at approximately 2 - 5 mm/minute.

Increased extracellular potassium ion concentration and excitatory glutamate contribute to the initiation and propagation of cortical spreading depression, which is the underlying cause of migraine aura.

Chapter 6

Headache (Symptom of Migraine)

Headache	
ICD-10	G43.-G44., R51.
ICD-9	339, 784.0
DiseasesDB	19825
MedlinePlus	003024
eMedicine	neuro/517 neuro/70
MeSH	D006261

A **headache** or **cephalgia** is pain anywhere in the region of the head or neck. It can be a symptom of a number of different conditions of the head and neck. The brain tissue itself is not sensitive to pain because it lacks pain receptors. Rather, the pain is caused by disturbance of the pain-sensitive structures around the brain. Several areas of the head and neck have these pain-sensitive structures, which are divided in two categories: within the cranium (blood vessels, meninges, and the cranial nerves) and outside the cranium (the periosteum of the skull, muscles, nerves, arteries and veins, subcutaneous tissues, eyes, ears, sinuses and mucous membranes).

There are a number of different classification systems for headaches. The most well-recognized is that of the International Headache Society. Treatment of a headache depends on the underlying etiology or cause, but commonly involves analgesics.

Classification

Headaches are most thoroughly classified by the International Headache Society's International Classification of Headache Disorders (ICHD), which published the second edition in 2004. This classification is accepted by the WHO.

Other classification systems exist. One of the first published attempts was in 1951. The National Institutes of Health developed a classification system in 1962.

ICHD-2

The International Classification of Headache Disorders (ICHD) is an in-depth hierarchical classification of headaches published by the International Headache Society. It contains explicit (operational) diagnostic criteria for headache disorders. The first version of the classification, ICHD-1, was published in 1988. The current revision, ICHD-2, was published in 2004.

The classification uses numeric codes. The top, one-digit diagnostic level includes 13 headache groups. The first four of these are classified as primary headaches, groups 5-12 as secondary headaches, cranial neuralgia, central and primary facial pain and other headaches for the last two groups.

The ICHD-2 classification defines migraines, tension-types headaches, cluster headache and other trigeminal autonomic cephalalgias as the main types of primary headaches. Also, according to the same classification, headaches due to stabbing, cough, exertion and sexual activity are classified as primary headaches. The daily-persistent headaches along with the hypnic headache and thunderclap headaches are considered primary headaches as well.

Secondary headaches are classified based on their etiology and not on their symptoms. According to the ICHD-2 classification, the main types of secondary headaches include those that are due to head or neck trauma such as whiplash injury, intracranial hematoma, post craniotomy or other head or neck injury. Headaches caused by cranial or cervical vascular disorders such as ischemic stroke and transient ischemic attack, non-traumatic intracranial hemorrhage, vascular malformations or arteritis are also defined as secondary headaches. This type of headaches may also be caused by cerebral venous thrombosis or different intracranial vascular disorders. Other secondary headaches are those due to intracranial disorders that are not vascular such as low or high pressure of the cerebrospinal fluid pressure, non-infectious inflammatory disease, intracranial neoplasm, epileptic seizure or other types of disorders or diseases that are intracranial but that are not associated with the vasculature of the central nervous system. ICHD-2 classifies headaches that are caused by the ingestion of a certain substance or by its withdrawal as secondary headaches as well. This type of headache may result from the overuse of some medications or by exposure to some substances. HIV/AIDS, intracranial infections and systemic infections may also cause secondary headaches. The ICHD-2 system of classification includes the headaches associated with homeostasis disorders in the category of secondary headaches. This means that headaches caused by dialysis, high blood pressure, hypothyroidism, and cephalalgia and even fasting are considered secondary headaches. Secondary headaches, according to the same classification system, can also be due to the injury of any of the facial structures including teeth, jaws, or temporomandibular joint. Headaches caused by psychiatric disorders such as somatization or psychotic disorders are also classified as secondary headaches.

The ICHD-2 classification puts cranial neuralgias and other types of neuralgia in a different category. According to this system, there are 19 types of neuralgias and

headaches due to different central causes of facial pain. Moreover, the ICHD-2 includes a category that contains all the headaches that cannot be classified.

Although the ICHD-2 is the most complete headache classification there is and it includes frequency in the diagnostic criteria of some types of headaches (primarily primary headaches), it does not specifically code frequency or severity which are left at the discretion of the examiner.

NIH

The NIH classification consists of brief definitions of a limited number of headaches.

The NIH system of classification is more succinct and only describes five categories of headaches. In this case, primary headaches are those that do not show organic or structural etiology. According to this classification, headaches can only be vascular, myogenic, cervicogenic, traction and inflammatory.

Differential diagnosis

There are over 200 types of headache, and the causes range from harmless to life-threatening. The description of the headache, together with findings on neurological examination, determines the need for any further investigations and the most appropriate treatment.

Typical causes

The most common types of headache are the "primary headache disorders", such tension-type headache and migraine. They have typical features; migraine, for example, tends to be pulsating in character, affecting one side of the head, associated with nausea, disabling in severity, and usually lasts between 3 hours and 3 days. Rarer primary headache disorders are trigeminal neuralgia (a shooting face pain), cluster headache (severe pains that occur together in bouts), and hemicrania continua (a continuous headache on one side of the head).

Secondary causes

Headaches may be caused by problems elsewhere in the head or neck. Some of these are not harmful, such as cervicogenic headache (pain arising from the neck muscles). Medication overuse headache may occur in those using excessive painkillers for headaches, parodoxically causing worsening headaches.

A number of characteristics make it more likely that the headache is due to potentially dangerous secondary causes; some of these may be life-threatening or cause long-term damage. A number of "red flag" symptoms therefore means that a headache warrants further investigations, usually by a specialist. The red flag symptoms are a new or different headache in someone over 50 years old, headache that develops within minutes

(thunderclap headache), inability to move a limb or abnormalities on neurological examination, mental confusion, being woken by headache, headache that worsens with changing posture, headache worsened by exertion or Valsalva manoeuvre (coughing, straining), visual loss or visual abnormalities, jaw claudication (jaw pain on chewing that resolves afterwards), neck stiffness, fever, and headaches in people with HIV, cancer or risk factors for thrombosis.

"Thunderclap headache" may be the only symptom of subarachnoid hemorrhage, a form of stroke in which blood accumulates around the brain, often from a ruptured brain aneurysm. Headache with fever may be caused by meningitis, particularly if there is meningism (inability to flex the neck forward due to stiffness), and confusion may be indicative of encephalitis (inflammation of the brain, usually due to particular viruses). Headache that is worsened by straining or a change in position may be caused by increased pressure in the skull; this is often worse in the morning and associated with vomiting. Raised intracranial pressure may be due to brain tumors, idiopathic intracranial hypertension (IIH, more common in younger overweight women) and occasionally cerebral venous sinus thrombosis. Headache together with weakness in part of the body may indicate a stroke (particularly intracranial hemorrhage or subdural hematoma) or brain tumor. Headache in older people, particularly when associated with visual symptoms or jaw claudication, may indicate giant cell arteritis (GCA), in which the blood vessel wall is inflamed and obstructs blood flow. Carbon monoxide poisoning may lead to headaches as well as nausea, vomiting, dizziness, muscle weakness and blurred vision. Angle closure glaucoma (acute raised pressure in the eyeball) may lead to headache, particularly around the eye, as well as visual abnormalities, nausea, vomiting and a red eye with a dilated pupil.

Pathophysiology

The brain in itself is not sensitive to pain, because it lacks pain receptors. However, several areas of the head and neck do have nociceptors, and can thus sense pain. These include the extracranial arteries, large veins, cranial and spinal nerves, head and neck muscles and the meninges.

Headache often results from traction to or irritation of the meninges and blood vessels. The nociceptors may also be stimulated by other factors than head trauma or tumors and cause headaches. Some of these include stress, dilated blood vessels and muscular tension. Once stimulated, a nociceptor sends a message up the length of the nerve fiber to the nerve cells in the brain, signaling that a part of the body hurts.

It has been suggested that the level of endorphins in one's body may have a great impact on how people feel headaches. Thus, it is believed that people who suffer from chronic headaches or severe headaches have lower levels of endorphins compared to people who do not complain of headaches.

Primary headaches are even more difficult to understand than secondary headaches. Although the pathophysiology of migraines, cluster headaches and tension headaches is

still not well understood, there have been different theories over time which attempt to provide an explanation of what exactly happens within the brain when individuals suffer from headaches. One of the oldest such theories is referred to as the vascular theory which was developed in the middle of the 20th century. The vascular theory was proposed by Wolff and it described the intracranial vasoconstriction as being responsible for the aura of the migraine. The headache was believed to result from the subsequent rebound of the dilatation of the blood vessels which led to the activation of the perivascular nociceptive nerves. The developers of this theory took into consideration the changes that occur within the blood vessels outside the cranium when a migraine attack occurs and other data that was available at that time including the effect of vasodilators and vasoconstrictors on headaches.

The neurovascular approach towards primary headaches is accepted by most specialists nowadays. According to this newer theory, migraines are triggered by a complex series of neural and vascular events. Different studies concluded that individuals who suffer from migraines but not from headache have a state of neuronal hyperexcitability in the cerebral cortex, especially in the occipital cortex. People who are more susceptible to experience migraines without headache are those who have a family history of migraines, women, and women who are experiencing hormonal changes or are taking birth control pills or are prescribed hormone replacement therapy.

Headaches in children

Children can suffer from the same types of headaches as adults do although their symptoms may vary. Some kinds of headaches include: tension headaches, migraines, chronic daily headaches, cluster headache and sinuses headaches. It is actually common for headaches to start in childhood or adolescence, for instance, 20% of adults who suffer headaches report that their headaches started before age 10 while 50% report they started before age 20. The incidence of headaches in children and adolescents is very common. One study reported that 56% of boys and 74% of girls between 12 and 17 indicated having experienced a form of headache within the past month.

The causes of headaches in children include either one factor or a combination of factors. Some of the most common factors include: genetic predisposition, especially in the case of migraine; head trauma, produced by accidental falls; illness and infection, for example in the presence of ear or sinus infection as well as colds and flu; environmental factors, which include weather changes; emotional factors, such as stress, anxiety, and depression; foods and beverages, caffeine or food additives; change in sleep or routine pattern; loud noises. Also, excess physical activity or sun may be a trigger specifically of migraine.

Although most cases of headaches in children are considered to be benign, when they are accompanied with other symptoms such as speech problems, muscle weakness, and loss of vision, a more serious underlying cause can be suspected. They include: hydrocephalus, meningitis, encephalitis, abscess, hemorrhage, tumor, blood clots, and

head trauma. In these cases, the headache evaluation may include CT scan or MRI in order to look for possible structural disorders of the central nervous system.

Some measures can help prevent headaches in children. Some of them are: drinking plenty of water throughout the day; avoiding caffeine; getting enough and regular sleep; eating balanced meals at the proper times; and reducing stress and excess of activities.

Diagnosis approach

The American College of Emergency Physicians have guidelines on the evaluation and management of adult patients who have a nontraumatic headache of acute onset.

While, statistically, headaches are most likely to be primary (non serious and self-limiting), some specific secondary headache syndromes may demand specific treatment or may be warning signals of more serious disorders. Differentiating between primary and secondary headaches can be difficult.

As it is often difficult for patients to recall the precise details regarding each headache, it is often useful for the sufferer to fill-out a "headache diary" detailing the characteristics of the headache.

Imaging

When the headache does not clearly fit into one of the recognized primary headache syndromes or when atypical symptoms or signs are present then further investigations are justified. Neuroimaging (noncontrast head CT) is recommended if there are new neurological problems such as decreased level of consciousness, one sided weakness, pupil size difference, etc. or if the pain is of sudden onset and severe, or if the person is known HIV positive. People over the age of 50 years may also warrant a CT scan.

Treatment

Acute headaches

Not all headaches require medical attention, and most respond with simple analgesia (painkillers) such as paracetamol/acetaminophen or non-steroidal anti-inflammatory drugs like aspirin, ibuprofen, or diclofenac.

Chronic headaches

In recurrent unexplained headaches keeping a "headache diary" with entries on type of headache, associated symptoms, precipitating and aggravating factors may be helpful. This may reveal specific patterns, such as an association with medication, menstruation or absenteeism or with certain foods. It was reported in March 2007 by two separate teams of researchers that stimulating the brain with implanted electrodes appears to help ease the pain of cluster headaches.

Acupuncture has been found to be beneficial in chronic headaches of both tension type and migraine type. Whether or not there is a difference between true acupuncture and sham acupuncture however is yet to be determined.

One type of treatment, however, is usually not sufficient for chronic sufferers and they may have to find a variety of different ways of managing, living with, and seeking treatment of chronic daily headache pains.

There are however two types of treatment for chronic headaches meaning acute abortive treatment and preventive treatment. Whereas the first is aimed to relieve the symptoms immediately, the latter is focused on controlling the headaches that are chronic. From this reason, the acute treatment is commonly and effectively used in treating migraines and the preventive treatment is the usual approach in managing chronic headaches. The primary goal of preventive treatment is to reduce the frequency, severity, and duration of headaches. This type of treatment involves taking medication on a daily basis for at least 3 months and in some cases, for over 6 months. The medication used in preventive treatment is normally chosen based on the other conditions that the patient is suffering from. Generally, medication in preventive treatment starts at the minimum dosage which increases gradually until the pain is relieved and the goal achieved or until side effects appear.

To date, only amitriptyline, fluoxetine, gabapentin, tizanidine, topiramate, and botulinum toxin type A (BoNTA) have been evaluated as "prophylactic treatment of chronic daily headache in randomized, double-blind, placebo-controlled or active comparator-controlled trials. Antiepileptics can be used as preventative treatment of chronic daily headache and includes Valproate.

Psychological treatments are usually considered in comorbid patients or in those who are unresponsive to the medication.

Epidemiology

During a given year, 90% of people suffer from headaches. Of the ones seen in the ER, about 1% have a serious underlying problem.

Primary headaches account for more than 90% of all headache complaints, and of these, episodic tension-type headache is the most common.

It is estimated that women are three folds more prone than men to suffer from migraines. Also, the prevalence of this particular type of headache seems to vary depending on the specific area of the world where one lives. However, migraines appear to be experienced by 12% to 18% of the population.

Cluster headaches are thought to be affecting less than 0.5% of the population, though their prevalence is hard to estimate because they are often mistaken as a sinusal problem.

However, according to the existent data, cluster headaches are more likely to occur in men than women, given that the condition tends to affect 5 to 8 times more men.

History

The first recorded classification system that resembles the modern ones was published by Thomas Willis, in *De Cephalagia* in 1672. In 1787 Christian Baur generally divided headaches into idiopathic (primary headaches) and symptomatic (secondary ones), and defined 84 categories.

Chapter 7

Nausea and Vomiting (Symptoms of Migraine)

Nausea

Nausea (Latin *nausea*, from Greek ναυσία, *nausiē*, "motion sickness", or "wamble"), is a sensation of unease and discomfort in the upper stomach with an involuntary urge to vomit. An attack of nausea is known as a **qualm**.

The most common cause is motion sickness, most often in automobiles, followed by gastroenteritis (a stomach infection) or food poisoning but nausea also frequently occurs as a medication side effect and in pregnancy. There are some medications, called antiemetics, that improve symptoms of nausea, including metoclopramide and ondansetron.

Differential diagnosis

The causes of nausea are many. One organization listed 700 in 2009. Gastrointestinal infections (37%) and food poisoning are the two most common causes. While side effects from medications (3%) and pregnancy are also relatively frequent. In 10% of people the cause remains unknown.

Food poisoning

Food poisoning usually causes an abrupt onset of nausea and vomiting one to six hours after ingestion of contaminated food and lasts for one to two days. It is due to toxins produced by bacteria in the food.

Medications

Most medications can potentially cause nausea. Some of the most frequently associated include chemotherapy regimens and general anaesthetic agents.

Pregnancy

Nausea or "morning sickness" is a common symptom of pregnancy. In the first trimester nearly 80% of women have some degree of nausea. Pregnancy should therefore be considered as a possible cause of nausea in any women of child bearing age. While usually it is mild and self limiting severe cases known as hyperemesis gravidarum may require treatment.

Disequilibrium

A number of conditions involving balance such as motion sickness and vertigo can lead to nausea and vomiting.

Potentially serious

While most causes of nausea are not serious some serious causes do occur. These include: diabetic ketoacidosis, surgical problems (pancreatitis, small bowel obstruction, meningitis, appendicitis, cholecystitis), Addisonian crisis, Choledocholithiasis (from gallstones) and hepatitis, signs of carbon monoxide poison among others.

Diagnostic approach

Often no investigations are needed, however basic lab tests may be appropriate. If a bowel obstruction is considered, abdominal x-rays may be useful.

Treatment

If dehydration is present, rehydration with oral electrolyte solutions is preferred. If this is not effective, intravenous rehydration may be required.

Medications

Dimenhydrinate (Gravol) is an inexpensive and effective medication for preventing postoperative nausea and vomiting. Meclozine is another antihistamine antiemetic. In certain people, cannabinoids may be effective in reducing chemotherapy associated nausea and vomiting. Ondansetron (Zofran) is effective for nausea and vomiting but is expensive. Pyridoxine or metoclopramide are the first line treatments for pregnancy related nausea and vomiting. Medical marijuana may be prescribed where allowed for certain indication.

Prognosis

While short-term nausea and vomiting are generally harmless, they may sometimes indicate a more serious condition. When associated with prolonged vomiting, it may lead to dehydration and/or dangerous electrolyte imbalances.

Epidemiology

Nausea and or vomiting is the main complaint in 1.6% of visits to family physicians in Australia. However only 25% of people with nausea visit their family physician. It is most common in those 15–24 years old and less common in other ages.

Vomiting

Vomiting (known medically as **emesis** and informally as **throwing up** and a number of other terms) is the forceful expulsion of the contents of one's stomach through the mouth and sometimes the nose. Vomiting can occur due to a wide variety of conditions; it may present as a specific response to ailments like gastritis or poisoning, or as a non-specific sequela of disorders ranging from brain tumors and elevated intracranial pressure to overexposure to ionizing radiation. The feeling that one is about to vomit is called nausea, which usually precedes, but does not always lead to, vomiting. Antiemetics are sometimes necessary to suppress nausea and vomiting, and, in severe cases where dehydration develops, intravenous fluid may need to be administered to replace fluid volume.

Vomiting is different from regurgitation, although the two terms are often used interchangeably. Regurgitation is the return of undigested food back up the esophagus to the mouth, without the force and displeasure associated with vomiting. The causes of vomiting and regurgitation are generally different.

Complications

Aspiration of vomit

Vomiting can be dangerous if the gastric content gets into the respiratory tract. Under normal circumstances the gag reflex and coughing will prevent this from occurring, however these protective reflexes are compromised in persons under the influences of certain substances such as alcohol or anesthesia. The individual may choke and asphyxiate or suffer an aspiration pneumonia.

Dehydration and electrolyte imbalance

Prolonged and excessive vomiting will deplete the body of water (dehydration) and may alter the electrolyte status. Gastric vomiting leads to the loss of acid (protons) and chlorine directly. Combined with the resulting alkaline tide, this leads to hypochloremic metabolic alkalosis (low chloride levels together with high HCO_3 and CO_2 and increased blood pH) and often hypokalemia (potassium depletion). The hypokalemia is an indirect result of the kidney compensating for the loss of acid. With the loss of intake of food the

individual may eventually become cachectic. A less frequent occurrence results from a vomiting of intestinal contents, including bile acids and HCO_3^- which can lead to metabolic acidosis.

Mallory-Weiss tear

Repeated or profuse vomiting may cause erosions to the esophagus or small tears in the esophageal mucosa (Mallory-Weiss tear). This may become apparent if fresh red blood is mixed with vomit after several episodes.

Dentistry

Recurrent vomiting, such as observed in bulimia nervosa, may lead to destruction of the tooth enamel due to the acidity of the vomit. Digestive enzymes can also have a negative effect on oral health, by degrading the tissue of the gums.

Pathophysiology

Receptors on the floor of the fourth ventricle of the brain represent a chemoreceptor trigger zone, known as the area postrema, stimulation of which can lead to vomiting. The area postrema is a circumventricular organ and as such lies outside the blood-brain barrier; it can therefore be stimulated by blood-borne drugs that can stimulate vomiting or inhibit it.

There are various sources of input to the vomiting center:

- The chemoreceptor trigger zone at the base of the fourth ventricle has numerous dopamine D_2 receptors, serotonin 5-HT_3 receptors, opioid receptors, acetylcholine receptors, and receptors for substance P. Stimulation of different receptors are involved in different pathways leading to emesis, in the final common pathway substance P appears to be involved.
- The vestibular system which sends information to the brain via cranial nerve VIII (vestibulocochlear nerve). It plays a major role in motion sickness and is rich in muscarinic receptors and histamine H_1 receptors.
- Cranial nerve X (vagus nerve), which is activated when the pharynx is irritated, leading to a gag reflex.
- Vagal and enteric nervous system inputs that transmit information regarding the state of the gastrointestinal system. Irritation of the GI mucosa by chemotherapy, radiation, distention, or acute infectious gastroenteritis activates the 5-HT_3 receptors of these inputs.
- The CNS mediates vomiting arising from psychiatric disorders and stress from higher brain centers.

The vomiting act encompasses three types of outputs initiated by the chemoreceptor trigger zone: Motor, parasympathetic nervous system (PNS), and sympathetic nervous system (SNS). They are as follows:

- Increased salivation to protect the enamel of teeth from stomach acids (excessive vomiting leads to dental erosion). This is part of the PNS output.
- A deep breath is taken to avoid aspiration of vomit.
- Retroperistalsis, starting from the middle of the small intestine, sweeping up the contents of the digestive tract into the stomach, through the relaxed pyloric sphincter.
- A lowering of intrathoracic pressure (by inspiration against a closed glottis), coupled with an increase in abdominal pressure as the abdominal muscles contract, propels stomach contents into the esophagus as the lower esophageal sphincter relaxes. The stomach itself does not contract in the process of vomiting except for at the angular notch, nor is there any retroperistalsis in the esophagus.
- Vomiting is ordinarily preceded by retching.
- Vomiting also initiates an SNS response causing both sweating and increased heart rate.

The neurotransmitters that regulate vomiting are poorly understood, but inhibitors of dopamine, histamine, and serotonin are all used to suppress vomiting, suggesting that these play a role in the initiation or maintenance of a vomiting cycle. Vasopressin and neurokinin may also participate.

Phases

The vomiting act has two phases. In the retching phase, the abdominal muscles undergo a few rounds of coordinated contractions together with the diaphragm and the muscles used in respiratory inspiration. For this reason, an individual may confuse this phase with an episode of violent hiccups. In this retching phase nothing has yet been expelled. In the next phase, also termed the expulsive phase, intense pressure is formed in the stomach brought about by enormous shifts in both the diaphragm and the abdomen. These shifts are, in essence, vigorous contractions of these muscles that last for extended periods of time - much longer than a normal period of muscular contraction. The pressure is then suddenly released when the upper esophageal sphincter relaxes resulting in the expulsion of gastric contents. For people not in the habit of exercising the abdominal muscles, they may be painful for the next few days. The relief of pressure and the release of endorphins into the bloodstream after the expulsion causes the vomiter to feel better.

Contents

Gastric secretions and likewise vomit are highly acidic. Recent food intake will be reflected in the gastric vomit. Irrespective of the content, vomit tends to be malodorous.

The content of the *vomitus* (vomit) may be of medical interest. Fresh blood in the vomit is termed hematemesis ("blood vomiting"). Altered blood bears resemblance to coffee grounds (as the iron in the blood is oxidized) and, when this matter is identified, the term "coffee ground vomiting" is used. Bile can enter the vomit during subsequent heaves due to duodenal contraction if the vomiting is severe. Fecal vomiting is often a consequence of intestinal obstruction or a gastrocolic fistula and is treated as a warning sign of this

potentially serious problem ("signum mali ominis"); such vomiting is sometimes called "miserere."

If the vomiting reflex continues for an extended period with no appreciable vomitus, the condition is known as *non-productive emesis* or *dry heaves*, which can be painful and debilitating.

Color of vomit

- Bright red in the vomit suggests bleeding from the oesophagus
- Dark red vomit with liver-like clots suggests profuse bleeding in the stomach, such as from a perforated ulcer
- Coffee ground-like vomit suggests less severe bleeding in the stomach, because the gastric acid has had time to change the composition of the blood
- Yellow vomit suggests bile. This indicates that the pyloric valve is open and bile is flowing into the stomach from the duodenum. (This is more common in older people.)

Differential diagnosis

Vomiting may be due to a large number of causes, and protracted vomiting has a long differential diagnosis.

Digestive tract

Causes in the digestive tract

- Gastritis (inflammation of the gastric wall, usually by viruses)
- Gastroenteritis
- Pyloric stenosis (in babies, this typically causes a very forceful "projectile vomiting" and is an indication for urgent surgery)
- Bowel obstruction
- Overeating
- Acute abdomen and/or peritonitis
- Ileus
- Food allergies (often in conjunction with hives or swelling)
- Cholecystitis, pancreatitis, appendicitis, hepatitis
- Food poisoning
- In children, it can be caused by an allergic reaction to cow's milk proteins (Milk allergy or lactose intolerance)

Sensory system and brain

Causes in the sensory system

- Movement: motion sickness (which is caused by overstimulation of the labyrinthine canals of the ear)
- Ménière's disease

Causes in the brain

- Concussion
- Cerebral hemorrhage
- Migraine
- Brain tumors, which can cause the chemoreceptors to malfunction
- Benign intracranial hypertension and hydrocephalus

Metabolic disturbances (these may irritate both the stomach and the parts of the brain that coordinate vomiting)

- Hypercalcemia (high calcium levels)
- Uremia (urea accumulation, usually due to renal failure)
- Adrenal insufficiency
- Hypoglycemia
- Hyperglycemia

Pregnancy

- Hyperemesis, Morning sickness

Drug reaction (vomiting may occur as an acute somatic response to)

- alcohol (being sick while being drunk or being sick the next morning, suffering from the after-effects, i.e., the hangover).
- opioids
- selective serotonin reuptake inhibitors
- many chemotherapy drugs
- some entheogens (such as peyote or ayahuasca)

Illness (sometimes colloquially known as "stomach flu"—a broad name that refers to gastric inflammation caused by a range of viruses and bacteria.)

- Norovirus (Formerly Norwalk virus or Norwalk agent)
- Swine Flu

Emetics

An *emetic*, such as syrup of ipecac, is a substance that induces vomiting when administered orally or by injection. An emetic is used medically where a substance has been ingested and must be expelled from the body immediately (for this reason, many toxic and easily digestible products such as rat poison contain an emetic). Inducing vomiting can remove the substance before it is absorbed into the body. Ipecac abuse can cause detrimental health effects.

Salt water and mustard water have been used since ancient times as emetics. Care must be taken with salt, as excessive intake can potentially be harmful.

Copper sulfate was also used in the past as an emetic. It is now considered too toxic for this use.

Social cues

It is quite common that, when one person vomits, others nearby will become nauseated, particularly when smelling the vomit of others, often to the point of vomiting themselves. It is believed that this is an evolved trait among primates. Many primates in the wild will tend to browse for food in small groups. Should one member of the party react adversely to some ingested food, it may be advantageous (in a survival sense) for other members of the party also to vomit. This tendency in human populations has been observed at drinking parties, where excessive consumption of alcoholic beverages may result in a number of party members vomiting nearly simultaneously, this being triggered by the initial vomiting of a single member of the party.

Intense vomiting in ayahuasca ceremonies is a common phenomenon. However, people who experience "la purga" after drinking ayahuasca, in general, regard the practice as both a physical and spiritual cleanse and often come to welcome it. It has been suggested that the consistent emetic effects of ayahuasca — in addition to its many other therapeutic properties — was of medicinal benefit to indigenous peoples of the Amazon, in helping to clear parasites from the gastrointestinal system.

There have also been documented cases of a single ill and vomiting individual inadvertently causing others to vomit, when they are especially fearful of also becoming ill, through a form of mass hysteria.

Context

Most people try to contain their vomit by vomiting into a sink, toilet, or trash can, as both the act and the vomit itself are widely considered embarrassing; vomit is also difficult to clean. On airplanes and boats, special bags are supplied for sick passengers to vomit into. A special disposable bag containing absorbent material that solidifies the vomit quickly is available, also, making it convenient and safe to keep (leakproof, puncture-resistant, odorless) until there is an opportunity to dispose of it conveniently.

People who vomit chronically (e.g., as part of an eating disorder such as bulimia nervosa) may devise various ways to hide this disorder.

Sound

An online study of people's responses to "horrible sounds" found vomiting "the most disgusting". Professor Cox of the University of Salford's Acoustic Research Centre said that "We are pre-programmed to be repulsed by horrible things such as vomiting, as it is

fundamental to staying alive to avoid nasty stuff." It is thought that disgust is triggered by the sound of vomiting to protect food from those possibly diseased nearby.

Miscellanea

- Self-induced
  - Eating disorders (anorexia nervosa or bulimia nervosa)
  - To eliminate an ingested poison (some poisons should not be vomited as they may be more toxic when inhaled or aspirated; it is better to ask for help before inducing vomiting)
  - Some people who are engaged in binge drinking will induce vomiting in order to make room in their stomachs for further alcohol consumption.
  - People suffering from nausea may induce vomiting in hopes of feeling better.
- After surgery (postoperative nausea and vomiting)
- Disagreeable sights, smells or thoughts (such as decayed matter, others' vomit, thinking of vomiting), etc.
- Extreme pain, such as intense headache or myocardial infarction (heart attack)
- Violent emotions
- Cyclic vomiting syndrome (a poorly-understood condition with attacks of vomiting)
- High doses of ionizing radiation will sometimes trigger a vomit reflex in the victim
- Violent fits of coughing, hiccups, or asthma
- Nervousness
- Anxiety
- Overexertion (doing too much strenuous exercise can lead to vomiting shortly afterwards).
- Rumination syndrome, an underdiagnosed and poorly understood disorder that causes sufferers to regurgitate food shortly after ingestion.

Treatment

An antiemetic is a drug that is effective against vomiting and nausea. Antiemetics are typically used to treat motion sickness and the side-effects of medications such as opioids and chemotherapy.

Antiemetics act by inhibiting the receptor sites associated with emesis. Hence, anticholinergics, antihistamines, dopamine antagonists, serotonin antagonists, and cannabinoids are used as anti-emetics.

Epidemiology

Nausea and or vomiting is the main complaint in 1.6% of visits to family physicians in Australia.

Chapter 8

Pain

Pain

ICD-10	R52
ICD-9	338
DiseasesDB	9503
MedlinePlus	002164
MeSH	D010146

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." It is the feeling common to such experiences as stubbing a toe, burning a finger, putting iodine on a cut, and bumping the "funny bone".

Pain motivates us to withdraw from potentially damaging situations, protect a damaged body part while it heals, and avoid those situations in the future. Most pain resolves promptly once the painful stimulus is removed and the body has healed, but sometimes pain persists despite removal of the stimulus and apparent healing of the body; and sometimes pain arises in the absence of any detectable stimulus, damage or disease.

Pain is the most common reason for physician consultation in the United States. It is a major symptom in many medical conditions, and can significantly interfere with a

person's quality of life and general functioning. Social support, hypnotic suggestion, excitement in sport or war, distraction, and appraisal can all significantly modulate pain's intensity or unpleasantness.

Classification

The International Association for the Study of Pain (IASP) classification system describes pain according to five categories: duration and severity, anatomical location, body system involved, cause, and temporal characteristics (intermittent, constant, etc.). This system has been criticized by Woolf and others as inadequate for guiding research and treatment, and an additional category based on neurochemical mechanism has been proposed.

Duration

Pain is usually transitory, lasting only until the noxious stimulus is removed or the underlying damage or pathology has healed, but some painful conditions, such as rheumatoid arthritis, peripheral neuropathy, cancer and idiopathic pain, may persist for years. Pain that lasts a long time is called *chronic*, and pain that resolves quickly is called *acute*. Traditionally, the distinction between *acute* and *chronic* pain has relied upon an arbitrary interval of time from onset; the two most commonly used markers being 3 months and 6 months since the onset of pain, though some theorists and researchers have placed the transition from acute to chronic pain at 12 months. Others apply *acute* to pain that lasts less than 30 days, *chronic* to pain of more than six months duration, and *subacute* to pain that lasts from one to six months. A popular alternative definition of *chronic pain*, involving no arbitrarily fixed durations is "pain that extends beyond the expected period of healing." Chronic pain may be classified as "malignant" (caused by cancer) or "benign" (non-malignant).

Region and system

Pain can be classed according to its location in the body, as in headache, low back pain and pelvic pain; or according to the body system involved, such as myofascial pain (emanating from skeletal muscles or the fibrous sheath surrounding them), rheumatic pain (emanating from the joints and surrounding tissue), neuropathic pain (caused by damage or illness affecting the somatosensory system), or vascular (pain from blood vessels).

Cause

The crudest example of classification by cause simply distinguishes "somatogenic" pain (arising from a perturbation of the body) from psychogenic pain (arising from a perturbation of the mind: when a thorough physical exam, imaging, and laboratory tests fail to detect the cause of pain, it is assumed to be the product of psychic conflict or psychopathology). Somatogenic pain is divided into "nociceptive" and "neuropathic".

Nociceptive

Nociceptive pain is caused by stimulation of peripheral nerve fibers that respond only to stimuli approaching or exceeding harmful intensity (nociceptors), and may be classified according to the mode of noxious stimulation; the most common categories being "thermal" (heat or cold), "mechanical" (crushing, tearing, etc.) and "chemical" (iodine in a cut, chili powder in the eyes).

Nociceptive pain may also be divided into "visceral," "deep somatic" and "superficial somatic" pain. *Visceral* pain originates in the viscera (organs) and often is extremely difficult to locate, and nociception from some visceral regions produces "referred" pain, where the sensation is located in an area distant from the site of the stimulus. *Deep somatic* pain is initiated by stimulation of nociceptors in ligaments, tendons, bones, blood vessels, fasciae and muscles, and is dull, aching, poorly-localized pain. Examples include sprains and broken bones. *Superficial* pain is initiated by activation of nociceptors in the skin or superficial tissues, and is sharp, well-defined and clearly located. Examples of injuries that produce superficial somatic pain include minor wounds and minor (first degree) burns.

Neuropathic

Neuropathic pain is caused by damage or disease affecting the central or peripheral portions of the nervous system involved in bodily feelings (the somatosensory system). Peripheral neuropathic pain is often described as “burning,” “tingling,” “electrical,” “stabbing,” or “pins and needles.” Bumping the "funny bone" elicits peripheral neuropathic pain.

Psychogenic

Psychogenic pain, also called *psychalgia* or *somatoform pain*, is pain caused, increased, or prolonged by mental, emotional, or behavioral factors. Headache, back pain, and stomach pain are sometimes diagnosed as psychogenic. Sufferers are often stigmatized, because both medical professionals and the general public tend to think that pain from a psychological source is not "real". However, specialists consider that it is no less actual or hurtful than pain from any other source.

People with long term pain frequently display psychological disturbance, with elevated scores on the Minnesota Multiphasic Personality Inventory scales of hysteria, depression and hypochondriasis (the "neurotic triad"). Some investigators have argued that it is this neuroticism that causes acute injuries to turn chronic, but clinical evidence points the other way, to chronic pain causing neuroticism. When long term pain is relieved by therapeutic intervention, scores on the neurotic triad and anxiety fall, often to normal levels. Self-esteem, often low in chronic pain patients, also shows improvement once pain has resolved.

“The term 'psychogenic' assumes that medical diagnosis is so perfect that all organic causes of pain can be detected; regrettably, we are far from such infallibility... All too often, the diagnosis of neurosis as the cause of pain hides our ignorance of many aspects of pain medicine.”
— Ronald Melzack, 1996.

Phantom pain

Phantom pain is pain from a part of the body that has been lost or from which the brain no longer receives signals. It is a type of neuropathic pain. Phantom limb pain is a common experience of amputees.

The prevalence of phantom pain in upper limb amputees is nearly 82%, and in lower limb amputees is 54%. One study found that eight days after amputation, 72 percent of patients had phantom limb pain, and six months later, 65 percent reported it. Some amputees experience continuous pain that varies in intensity or quality; others experience several bouts a day, or it may occur only once every week or two. It is often described as shooting, crushing, burning or cramping. If the pain is continuous for a long period, parts of the intact body may become sensitized, so that touching them evokes pain in the phantom limb, or phantom limb pain may accompany urination or defecation.

Local anesthetic injections into the nerves or sensitive areas of the stump may relieve pain for days, weeks or, sometimes permanently, despite the drug wearing off in a matter of hours; and small injections of hypertonic saline into the soft tissue between vertebrae produces local pain that radiates into the phantom limb for ten minutes or so and may be followed by hours, weeks or even longer of partial or total relief from phantom pain. Vigorous vibration or electrical stimulation of the stump, or current from electrodes surgically implanted onto the spinal cord all produce relief in some patients.

Work by Vilayanur S. Ramachandran using Mirror box therapy allows for illusions of movement and touch in a phantom limb which in turn cause a reduction in pain.

Paraplegia, the loss of sensation and voluntary motor control after serious spinal cord damage, may be accompanied by girdle pain at the level of the spinal cord damage, visceral pain evoked by a filling bladder or bowel, or, in five to ten per cent of paraplegics, phantom body pain in areas of complete sensory loss. Phantom body pain is initially described as burning or tingling but may evolve into severe crushing or pinching pain, fire running down the legs, or a knife twisting in the flesh. Onset may be immediate or may not occur until years after the disabling injury. Surgical treatment rarely provides lasting relief.

Pain asymbolia and insensitivty

The ability to experience pain is essential for protection from injury, and recognition of the presence of injury. Episodic analgesia may occur under special circumstances, such as

in the excitement of sport or war: a soldier on the battlefield may feel no pain for many hours from a traumatic amputation or other severe injury.

Although unpleasantness is an essential part of the IASP definition of pain, it is possible to induce a state described as intense pain devoid of unpleasantness in some patients, with morphine injection or psychosurgery. Such patients report that they have pain but are not bothered by it, they recognize the sensation of pain but suffer little, or not at all. Indifference to pain can also rarely be present from birth; these people have normal nerves on medical investigations, and find pain unpleasant, but do not avoid repetition of the pain stimulus.

Insensitivity to pain may also result from abnormalities in the nervous system. This is usually the result of acquired damage to the nerves, such as spinal cord injury, diabetes mellitus (diabetic neuropathy), or leprosy in countries where this is prevalent. These individuals are at risk of tissue damage due to undiscovered injury. People with diabetes-related nerve damage, for instance, sustain poorly healing foot ulcers as a result of decreased sensation.

A much smaller number of people are insensitive to pain due to an inborn abnormality of the nervous system, known as "congenital insensitivity to pain". Children with this condition incur carelessly repeated damage to their tongue, eyes, joints, skin, and muscles. They may attain adulthood, but have a reduced life expectancy. Most people with congenital insensitivity to pain have one of five hereditary sensory and autonomic neuropathies (which includes familial dysautonomia and congenital insensitivity to pain with anhidrosis).These conditions feature decreased sensitivity to pain together with other neurological abnormalties, particularly of the autonomic nervous system. A very rare syndrome with isolated congenital insensitivity to pain has been linked with mutations in the *SCN9A* gene, which codes for a sodium channel ($Na_v1.7$) necessary in conducting pain nerve stimuli.

Effect on psychological and psychosocial functioning

Experimental subjects challenged by acute pain and patients in chronic pain experience impairments in attention control, working memory, mental flexibility, problem solving, and information processing speed. Acute and chronic pain are also associated with increased depression, anxiety, fear, and anger.

"If I have matters right, the consequences of pain will include direct physical distress, unemployment, financial difficulties, marital disharmony, and difficulties in concentration and attention…"
—Harold Merskey 2000

Theory

Specificity

Descartes' pain pathway

In his 1664 *Treatise of Man,* René Descartes traced a pain pathway. "Particles of heat" (A) activate a spot of skin (B) attached by a fine thread (cc) to a valve in the brain (de) where this activity opens the valve, allowing the animal spirits to flow from a cavity (F) into the muscles that then flinch from the stimulus, turn the head and eyes toward the affected body part, and move the hand and turn the body protectively. The underlying premise of this model - that pain is the direct product of a noxious stimulus activating a dedicated pain pathway, from a receptor in the skin, along a thread or chain of nerve fibers to the pain center in the brain, to a mechanical behavioral response - remained the dominant perspective on pain until the mid-nineteen sixties.

Pattern

This "specificity theory" (specific pain receptor and pathway) was challenged by the theory, proposed initially in 1874 by Wilhelm Erb, that a pain signal can be generated by stimulation of *any* sensory receptor, provided the stimulation is intense enough: the pattern of stimulation (intensity over time and area), not the receptor type, determines

whether nociception occurs. Alfred Goldscheider (1894) proposed that over time, activity from many sensory fibers might accumulate in the dorsal horns of the spinal cord and begin to signal pain once a certain threshold of accumulated stimulation has been crossed. In 1953, Willem Noordenbos observed that a signal carried from the area of injury along large diameter "touch, pressure or vibration" fibers may inhibit the signal carried by the thinner "pain" fibers - the ratio of large fiber signal to thin fiber signal determining pain intensity; hence, we rub a smack. This was taken as a demonstration that pattern of stimulation (of large and thin fibers in this instance) modulates pain intensity.

Gate control

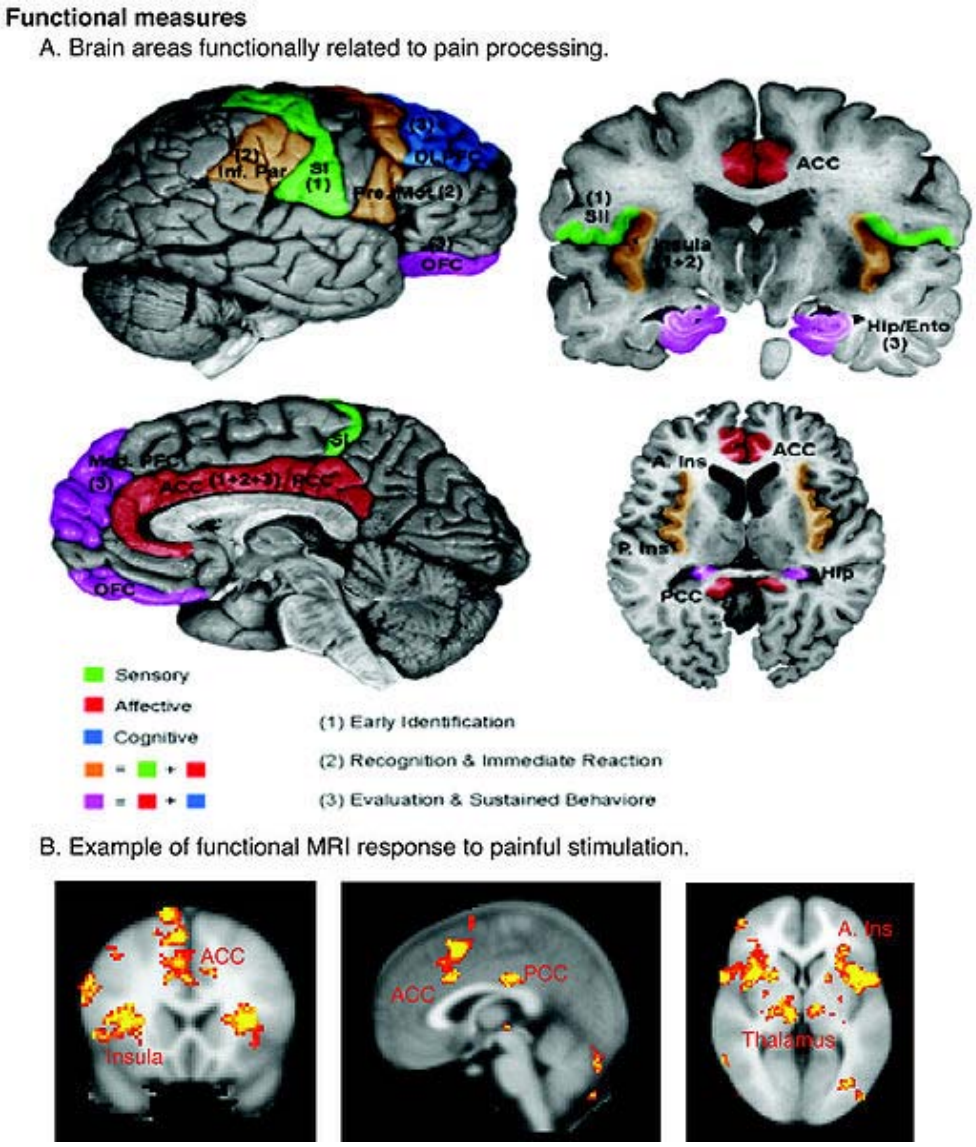
Melzack and Wall introduced their "gate control" theory of pain in the 1965 *Science* article "Pain Mechanisms: A New Theory". The authors proposed that thin (pain) and large diameter (touch, pressure, vibration) nerve fibers carry information from the site of injury to two destinations in the dorsal horn of the spinal cord: the "inhibitory" cells and the "transmission" cells. Signals from both thin and large diameter fibers excite the transmission cells, and when the output of the transmission cells exceeds a critical level, pain begins. The job of the inhibitory cells is to inhibit activation of the transmission cells. The transmission cells are the gate on pain, and inhibitory cells can shut the gate. When thin (pain) and large (touch, etc.) fibers, activated by a noxious event, excite a spinal cord transmission cell, they also act on its inhibitory cells. The thin fibers *impede* the inhibitory cells (tending to leave the gate open) while the large diameter fibers *excite* the inhibitory cells (tending to close the gate). So, the more large fiber activity relative to thin fiber activity coming from the inhibitory cell's receptive field, the less pain is felt. The authors had conceived a neural "circuit diagram" to explain why we rub a smack. They pictured not only a signal traveling from the site of injury to the inhibitory and transmission cells and up the spinal cord to the brain, but also a signal traveling from the site of injury directly up the cord to the brain (bypassing the inhibitory and transmission cells) where, depending on the state of the brain, it may trigger a signal back down the spinal cord to modulate inhibitory cell activity (and so pain intensity). This was the first theory to offer a physiological explanation for the previously reported effect of psychology on pain perception.

Dimensions

In 1968 Melzack and Casey described pain in terms of its three dimensions: "Sensory-discriminative" (sense of the intensity, location, quality and duration of the pain), "Affective-motivational" (unpleasantness and urge to escape the unpleasantness), and "Cognitive-evaluative" (cognitions such as appraisal, cultural values, distraction and hypnotic suggestion). They theorized that pain intensity (the sensory discriminative dimension) and unpleasantness (the affective-motivational dimension) are not simply determined by the magnitude of the painful stimulus, but “higher” cognitive activities (the cognitive-evaluative dimension) can influence perceived intensity and unpleasantness. Cognitive activities "may affect both sensory and affective experience or they may modify primarily the affective-motivational dimension. Thus, excitement in games or war appears to block both dimensions of pain, while suggestion and placebos

may modulate the affective-motivational dimension and leave the sensory-discriminative dimension relatively undisturbed." (p. 432) The paper ends with a call to action: "Pain can be treated not only by trying to cut down the sensory input by anesthetic block, surgical intervention and the like, but also by influencing the motivational-affective and cognitive factors as well." (p. 435)

Theory today



Regions of the cerebral cortex associated with pain

Wilhelm Erb's (1874) early pattern theory hypothesis, that a pain signal can be generated by intense enough stimulation of *any* sensory receptor, has been soundly disproved. The thin (A-delta and C) peripheral nerve fibers carry information regarding the state of the body to the spinal cord. Some of these thin fibers do not differentiate noxious from non-noxious stimuli, while others, nociceptors, respond only to painfully intense stimuli.

Because the A-delta fiber is thinly sheathed in an electrically insulating material (myelin), it carries its signal faster (2.5–35 m/s) than the unmyelinated C fiber (0.5–2.0 m/s). Pain evoked by the (faster) A-delta fibers is described as sharp and is felt first. This is followed by a duller pain, often described as burning, carried by the C fibers.

Spinal cord fibers dedicated to carrying A-delta fiber pain signals, and others dedicated to carrying C fiber pain signals up the spinal cord to the thalamus in the brain have been identified. Pain-related activity in the thalamus spreads to the insular cortex (thought to embody, among other things, the feeling that distinguishes pain from other homeostatic emotions such as itch and nausea) and anterior cingulate cortex (thought to embody, among other things, the motivational element of pain);and pain that is distinctly located also activates the primary and secondary somatosensory cortices.

One study has found that pain reduction due to non-noxious touch or vibration can result from activity within the cerebral cortex, with minimal contribution at the spinal level. Melzack and Casey's 1968 picture of the dimensions of pain is as influential today as ever, firmly framing theory and guiding research in the functional neuroanatomy and psychology of pain.

Evolutionary and behavioral role

Pain is part of the body's defense system, producing a reflexive retraction from the painful stimulus, and tendencies to protect the affected body part while it heals, and avoid that harmful situation in the future. It is an important part of animal life, vital to healthy survival. People with congenital insensitivity to pain have reduced life expectancy. Idiopathic pain (pain that persists after the trauma or pathology has healed, or that arises without any apparent cause), may be an exception to the idea that pain is helpful to survival, although some psychodynamic psychologists argue that such pain is psychogenic, enlisted as a protective distraction to keep dangerous emotions unconscious. It is not clear what the survival benefit of some extreme forms of pain (e.g. toothache) might be, and the intensity of some forms of pain (for example as a result of injury to fingernails or toenails) seems to be out of all proportion to any survival benefits.

Thresholds

In pain science, thresholds are measured by gradually increasing the intensity of a stimulus such as electric current or heat applied to the body. The pain perception threshold is the point at which the stimulus begins to hurt, and the pain tolerance threshold is reached when the subject acts to stop the pain.

Differences in pain perception and tolerance thresholds are associated with, among other factors, ethnicity, genetics, and sex. People of Mediterranean origin report as painful some radiant heat intensities that northern Europeans describe as warmth, and Italian women tolerate less intense electric shock than Jewish or Native American women. Some individuals in all cultures have significantly higher than normal pain perception and tolerance thresholds. For instance, patients who experience painless heart attacks have

higher pain thresholds for electric shock, muscle cramp and heat. Women have lower pain perception and tolerance thresholds than men, and this sex difference appears to apply to all ages, including newborn infants.

Assessment

A person's self report is the most reliable measure of pain, with health care professionals tending to underestimate severity. A definition of pain widely employed in nursing, emphasizing its subjective nature and the importance of believing patient reports, was introduced by Margo McCaffery in 1968: "Pain is whatever the experiencing person says it is, existing whenever he says it does". To assess intensity, the patient may be asked to locate their pain on a scale of 0 to 10, with 0 being no pain at all, and 10 the worst pain they have ever felt. Quality can be established by having the patient complete the McGill Pain Questionnaire indicating which words best describe their pain.

Multidimensional pain inventory

The Multidimensional Pain Inventory (MPI) is a questionnaire designed to assess the psychosocial state of a person with chronic pain. Analysis of MPI results by Turk and Rudy (1988) found three classes of chronic pain patient: "(a) dysfunctional, people who perceived the severity of their pain to be high, reported that pain interfered with much of their lives, reported a higher degree of psychological distress caused by pain, and reported low levels of activity; (b) interpersonally distressed, people with a common perception that significant others were not very supportive of their pain problems; and (c) adaptive copers, patients who reported high levels of social support, relatively low levels of pain and perceived interference, and relatively high levels of activity." Combining the MPI characterization of the person with their IASP five-category pain profile is recommended for deriving the most useful case description.

In nonverbal patients

When a person is non-verbal and cannot self report pain, observation becomes critical, and specific behaviors can be monitored as pain indicators. Behaviors such as facial grimacing and guarding indicate pain, as well as an increase or decrease in vocalizations, changes in routine behavior patterns and mental status changes. Patients experiencing pain may exhibit withdrawn social behavior and possibly experience a decreased appetite and decreased nutritional intake. A change in condition that deviates from baseline such as moaning with movement or when manipulating a body part, and limited range of motion are also potential pain indicators. In patients who possess language but are incapable of expressing themselves effectively, such as those with dementia, an increase in confusion or display of aggressive behaviors or agitation, may signal that discomfort exists, and further assessment is necessary.

Infants feel pain but they lack the language needed to report it, so communicate distress by crying. A non-verbal pain assessment should be conducted involving the parents, who

will notice changes in the infant not obvious to the health care provider. Pre-term babies are more sensitive to painful stimuli than full term babies.

Other barriers to reporting

An aging adult may not respond to pain in the way that a younger person would. Their ability to recognize pain may be blunted by illness or the use of multiple prescription drugs. Depression may also keep the older adult from reporting they are in pain. The older adult may also quit doing activities they love because it hurts too much. Decline in self-care activities (dressing, grooming, walking, etc.) may also be indicators that the older adult is experiencing pain. The older adult may refrain from reporting pain because they are afraid they will have to have surgery or will be put on a drug they become addicted to. They may not want others to see them as weak, or may feel there is something impolite or shameful in complaining about pain, or they may feel the pain is deserved punishment for past transgressions.

Cultural barriers can also keep a person from telling someone they are in pain. Religious beliefs may prevent the individual from seeking help. They may feel certain pain treatment is against their religion. They may not report pain because they feel it is a sign that death is near. Many people fear the stigma of addiction and avoid pain treatment so as not to be prescribed addicting drugs. Many Asians do not want to lose respect in society by admitting they are in pain and need help, believing the pain should be borne in silence, while other cultures feel they should report pain right away and get immediate relief. Gender can also be a factor in reporting pain. Gender differences are usually the result of social and cultural expectations, with women expected to be emotional and show pain and men stoic, keeping pain to themselves.

As an aid to diagnosis

Pain is a symptom of many medical conditions. Knowing the time of onset, location, intensity, pattern of occurrence (continuous, intermittent, etc.), exacerbating and relieving factors, and quality (burning, sharp, etc.) of the pain will help the examining physician to accurately diagnose the problem. For example, chest pain described as extreme heaviness may indicate myocardial infarction, while chest pain described as tearing may indicate aortic dissection.

Management

Inadequate treatment of pain is widespread throughout surgical wards, intensive care units, accident and emergency departments, in general practice, in the management of all forms of chronic pain including cancer pain, and in end of life care. This neglect is extended to all ages, from neonates to the frail elderly. African and Hispanic Americans are more likely than others to suffer needlessly in the hands of a physician; and women's pain is more likely to be undertreated than men's.

The International Association for the Study of Pain advocates that the relief of pain should be recognized as a human right, that chronic pain should be considered a disease in its own right, and that pain medicine should have the full status of a specialty. It is a specialty only in China and Australia at this time. Elsewhere, pain medicine is a subspecialty under disciplines such as anesthesiology, physiatry, neurology, palliative medicine and psychiatry.

Medication

Acute pain is usually managed with medications such as analgesics and anesthetics. Management of chronic pain, however, is much more difficult and may require the coordinated efforts of a pain management team, which typically includes medical practitioners, clinical psychologists, physiotherapists, occupational therapists, and nurse practitioners.

Sugar taken orally reduces the total crying time but not the duration of the first cry in newborns undergoing a painful procedure (a single lancing of the heel). It does not moderate the effect of pain on heart rate and a recent single study found that sugar did not significantly affect pain-related electrical activity in the brains of newborns one second after the heel lance procedure. Sweet oral liquid moderately reduces the incidence and duration of crying caused by immunization injection in children between one and twelve months of age.

Psychological

Individuals with more social support experience less cancer pain, take less pain medication, report less labor pain and are less likely to use epidural anesthesia during childbirth or suffer from chest pain after coronary artery bypass surgery.

Suggestion can significantly affect pain intensity. About 35% of people report marked relief after receiving a saline injection they believe to have been morphine. This "placebo" effect is more pronounced in people who are prone to anxiety, so anxiety reduction may account for some of the effect, but it does not account for all of the effect. Placebos are more effective in intense pain than mild pain; and they produce progressively weaker effects with repeated administration.

It is possible for many chronic pain sufferers to become so absorbed in an activity or entertainment that the pain is no longer felt, or is greatly diminished.

Cognitive behavioral therapy (CBT) is effective in reducing the suffering associated with chronic pain in some patients but the reduction in suffering is quite modest, and the CBT method employed seems to have no effect on outcome.

Alternative medicine

Pain is the most common reason for people to use complementary and alternative medicine. An analysis of the 13 highest quality studies of pain treatment with acupuncture, published in January 2009 in the *British Medical Journal*, concluded there is little difference in the effect of real, sham and no acupuncture. There is interest in the relationship between vitamin D and pain, but the evidence so far from controlled trials for such a relationship, other than in osteomalacia, is unconvincing.

A 2007 review of 13 studies found evidence for the efficacy of hypnosis in the reduction of pain in some conditions, though the number of patients enrolled in the studies was low, bringing up issues of power to detect group differences, and most lacked credible controls for placebo and/or expectation. The authors concluded that "although the findings provide support for the general applicability of hypnosis in the treatment of chronic pain, considerably more research will be needed to fully determine the effects of hypnosis for different chronic-pain conditions."

A 2003 meta-analysis of randomized clinical trials found that spinal manipulation was "more effective than sham therapy but was no more or less effective than general practitioner care, analgesics, physical therapy, exercise, or back school" in the treatment of low back pain.

Epidemiology

Pain is the main reason for visiting the emergency department in more than 50% of cases and is present in 30% of family practice visits. Several epidemiological studies from different countries have reported widely varying prevalence rates for chronic pain, ranging from 12-80% of the population. It becomes more common as people approach death. A study of 4,703 patients found that 26% had pain in the last two years of life, increasing to 46% in the last month.

A survey of 6,636 children (0-18 years of age) found that, of the 5,424 respondents, 54% had experienced pain in the preceding three months. A quarter reported having experienced recurrent or continuous pain for three months or more, and a third of these reported frequent and intense pain. The intensity of chronic pain was higher for girls, and girls' reports of chronic pain increased markedly between ages12 and 14.

Society and culture

The okipa ceremony as witnessed by George Catlin, circa 1835.

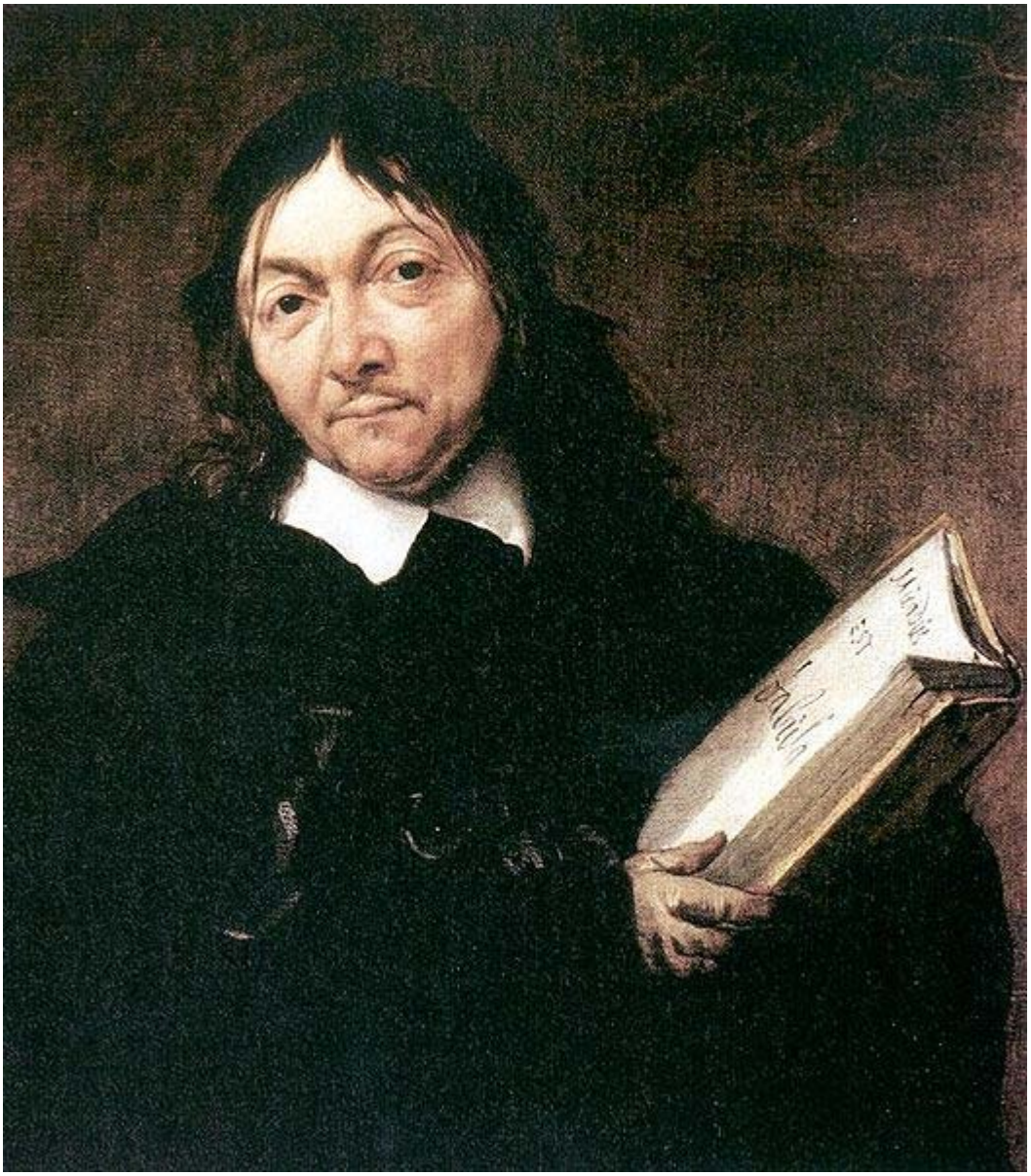
The nature or meaning of physical pain has been diversely understood by religious or secular traditions from antiquity to modern times.

Physical pain is an important political topic in relation to various issues, including pain management policy, drug control, animal rights or animal welfare, torture, pain compliance. In various contexts, the deliberate infliction of pain in the form of corporal punishment is used as retribution for an offence, or for the purpose of disciplining or reforming a wrongdoer, or to deter attitudes or behaviour deemed unacceptable. In some cultures, extreme practices such as mortification of the flesh or painful rites of passage are highly regarded.

Philosophy of pain is a branch of philosophy of mind that deals essentially with physical pain. Identity theorists assert that the mental state of pain is completely identical with some physiological state. Functionalists consider that pain as a mental state is constituted solely by its functional role, by its causal relations to other mental states, sensory inputs, and behavioral outputs.

More generally, it is often as a part of pain in the broad sense, i.e. suffering, that physical pain is dealt with in culture, religion, philosophy, or society.

In other animals



Portrait of René Descartes by Jan Baptist Weenix 1647-1649

The most reliable method for assessing pain in most humans is by asking a question: a person may report pain that cannot be detected by any known physiological measure. However, like infants (Latin *infans* meaning "unable to speak"), non-human animals cannot answer questions about whether they feel pain; thus the defining criterion for pain in humans cannot be applied to them. Philosophers and scientists have responded to this difficulty in a variety of ways. René Descartes for example argued that animals lack consciousness and therefore do not experience pain and suffering in the way that humans do. Bernard Rollin of Colorado State University, the principal author of two U.S. federal laws regulating pain relief for animals, writes that researchers remained unsure into the 1980s as to whether animals experience pain, and that veterinarians trained in the U.S.

before 1989 were simply taught to ignore animal pain. In his interactions with scientists and other veterinarians, he was regularly asked to "prove" that animals are conscious, and to provide "scientifically acceptable" grounds for claiming that they feel pain. Carbone writes that the view that animals feel pain differently is now a minority view. Academic reviews of the topic are more equivocal, noting that although the argument that animals have at least simple conscious thoughts and feelings has strong support, some critics continue to question how reliably animal mental states can be determined. The ability of invertebrate species of animals, such as insects, to feel pain and suffering is also unclear.

The presence of pain in an animal cannot be known for certain, but it can be inferred through physical and behavioral reactions. Specialists currently believe that all vertebrates can feel pain, and that certain invertebrates, like the octopus, might too. As for other animals, plants, or other entities, their ability to feel physical pain is at present a question beyond scientific reach, since no mechanism is known by which they could have such a feeling. In particular, there are no known nociceptors in groups such as plants, fungi, and most insects, except for instance in fruit flies.

In vertebrates, endogenous opioids are neurochemicals that moderate pain by interacting with opiate receptors. Opioids and opiate receptors occur naturally in crustaceans and, although at present no certain conclusion can be drawn, their presence indicates that lobsters may be able to experience pain. Opioids may mediate their pain in the same way as in vertebrates. Veterinary medicine uses, for actual or potential animal pain, the same analgesics and anesthetics as used in humans.

Etymology

First attested in English in 1297, the word *pain* comes from the Old French *peine*, in turn from Latin *poena*, "punishment, penalty" (in L.L. also "torment, hardship, suffering") and that from Greek "ποινή" (*poine*), generally "price paid", "penalty", "punishment".

Chapter 9

Chronic Pain and Psychogenic Pain

Chronic pain

	Chronic pain
ICD-10	R52.1-R52.2
ICD-9	338.2

Chronic pain has several different meanings in medicine. Traditionally, the distinction between *acute* and *chronic* pain has relied upon an arbitrary interval of time from onset; the two most commonly used markers being 3 months and 6 months since the initiation of pain, though some theorists and researchers have placed the transition from acute to chronic pain at 12 months. Others apply *acute* to pain that lasts less than 30 days, *chronic* to pain of more than six months duration, and *subacute* to pain that lasts from one to six months. A popular alternative definition of *chronic pain*, involving no arbitrarily fixed durations is "pain that extends beyond the expected period of healing."

Classification

Chronic pain may be divided into "nociceptive" (caused by activation of nociceptors), and "neuropathic" (caused by damage to or malfunction of the nervous system).

Nociceptive pain may be divided into "superficial somatic" and "deep", and *deep* pain into "deep somatic" and "visceral". *Superficial somatic* pain is initiated by activation of nociceptors in the skin or superficial tissues. *Deep somatic* pain is initiated by stimulation of nociceptors in ligaments, tendons, bones, blood vessels, fasciae and muscles, and is dull, aching, poorly-localized pain. *Visceral* pain originates in the viscera (organs). Visceral pain may be well-localized, but often it is extremely difficult to locate, and several visceral regions produce "referred" pain when injured, where the sensation is located in an area distant from the site of pathology or injury.

Neuropathic pain is divided into "peripheral" (originating in the peripheral nervous system) and "central" (origiiniting in the brain or spinal cord). Peripheral neuropathic pain

is often described as “burning,” “tingling,” “electrical,” “stabbing,” or “pins and needles.” Bumping the "funny bone" elicits peripheral neuropathic pain.

Pathophysiology

Under persistent activation nociceptive transmission to the dorsal horn may induce a wind up phenomenon. This induces pathological changes that lower the threshold for pain signals to be transmitted. In addition it may generate nonnociceptive nerve fibers to respond to pain signals. Nonnociceptive nerve fibers may also be able to generate and transmit pain signals. In chronic pain this process is difficult to reverse or eradicate once established.

Chronic pain of different etiologies has been characterized as a disease affecting brain structure and function. Magnetic Resonance Imaging studies have shown abnormal anatomical and functional connectivity, even during rest involving areas related to the processing of pain. Also, persistent pain has been shown to cause grey matter loss, reversible once the pain has resolved.

Management

Complete and sustained remission of many neuropathies and most idiopathic chronic pain (pain that extends beyond the expected period of healing, or chronic pain that has no known underlying pathology) is rarely achieved, but much can be done to reduce suffering and improve quality of life.

Pain management (also called pain medicine) is that branch of medicine employing an interdisciplinary approach to the relief of pain and improvement in the quality of life of those living with pain. The typical pain management team includes medical practitioners, clinical psychologists, physiotherapists, occupational therapists, and nurse practitioners. Acute pain usually resolves with the efforts of one practitioner; however, the management of chronic pain frequently requires the coordinated efforts of the treatment team.

Epidemiology

In a recent large-scale telephone survey of 15 European countries and Israel, 19% of respondents over 18 years of age had suffered pain for more than 6 months, including the last month, and more than twice in the last week, with pain intensity of 5 or more for the last episode, on a scale of 1(no pain) to 10 (worst imaginable). 4839 of these respondents with chronic pain were interviewed in depth. Sixty six percent scored their pain intensity at moderate (5–7), and 34% at severe (8–10); 46% had constant pain, 56% intermittent; 49% had suffered pain for 2–15 years; and 21% had been diagnosed with depression due to the pain. Sixty one percent were unable or less able to work outside the home, 19% had lost a job, and 13% had changed jobs due to their pain. Forty percent had inadequate pain management and less than 2% were seeing a pain management specialist.

Comorbidities and sequelae

Chronic pain is associated with higher rates of depression and anxiety. Sleep disturbance, and insomnia due to medication and illness symptoms are often experienced by those with chronic pain. Substance abuse is highly prevalent in some segments of the chronic pain population such as those with chronic headache. Chronic pain may contribute to decreased physical activity due to fear of exacerbating pain.

Psychology

Personality

Two of the most frequent personality profiles found in chronic pain patients by the Minnesota Multiphasic Personality Inventory (MMPI) are the *conversion V* and the *neurotic triad*. The conversion V personality, so called because the higher scores on MMPI scales 1 and 3, relative to scale 2, form a "V" shape on the graph, expresses exaggerated concern over body feelings, develops bodily symptoms in response to stress, and often fails to recognize their own emotional state, including depression. The neurotic triad personality, scoring high on scales 1, 2 and 3, also expresses exaggerated concern over body feelings and develops bodily symptoms in response to stress, but is demanding and complaining.

Some investigators have argued that it is this neuroticism that causes acute pain to turn chronic, but clinical evidence points the other way, to chronic pain causing neuroticism. When long term pain is relieved by therapeutic intervention, scores on the neurotic triad and anxiety fall, often to normal levels. Self-esteem, often low in chronic pain patients, also shows striking improvement once pain has resolved.

Effect on cognition

Chronic pain's impact on cognition is an under-researched area, but several tentative conclusions have been published. Most chronic pain patients complain of cognitive impairment, such as forgetfulness, difficulty with attention, and difficulty completing tasks. Objective testing has found that people in chronic pain tend to experience impairment in attention, memory, mental flexibility, verbal ability, speed of response in a cognitive task, and speed in executing structured tasks. In 2007, Shulamith Kreitler and David Niv advised clinicians to assess cognitive function in chronic pain patients in order to more precisely monitor therapeutic outcomes, and tailor treatment to address this aspect of the pain experience.

Psychogenic pain

Psychogenic pain	
ICD-10	F45.4
ICD-9	307.8
MedlinePlus	000922

Psychogenic pain, also called psychalgia, is physical pain that is caused, increased, or prolonged by mental, emotional, or behavioral factors.

Headache, back pain, or stomach pain are some of the most common types of psychogenic pain. It may occur, rarely, in persons with a mental disorder, but more commonly it accompanies or is induced by social rejection, broken heart, grief, love sickness, or other such emotional events.

Sufferers are often stigmatized, because both medical professionals and the general public tends to think that pain from psychological source is not "real". However, specialists consider that it is no less actual or hurtful than pain from other sources.

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, *or described in terms of such damage*" (emphasis added). In the note accompanying that definition, the following can be found about pain that happens for psychological reasons:

Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain.

Medicine refers also to psychogenic pain or psychalgia as a form of chronic pain under the name of *persistent somatoform pain disorder*. Causes may be linked to stress, unexpressed emotional conflicts, psychosocial problems, or various mental disorders. Some specialists believe that psychogenic chronic pain exists as a protective distraction to keep dangerous repressed emotions such as anger or rage unconscious.

It remains controversial, however, that chronic pain might arise purely from emotional causes. Treatment may include psychotherapy, antidepressants, analgesics, and other remedies that are used for chronic pain in general.

Chapter 10

Neuropathic Pain

"**Neuropathic pain** may arise as a consequence of a lesion or disease affecting the somatosensory system." It may be associated with abnormal sensations called dysesthesia, which occur spontaneously and allodynia that occurs in response to external stimuli. Neuropathic pain may have continuous and/or episodic (paroxysmal) components. The latter are likened to an electric shock. Common qualities include burning or coldness, "pins and needles" sensations, numbness and itching. Nociceptive pain is more commonly described as aching.

Up to 7% to 8% of the European population is affected and in 5% of persons it may be severe. Neuropathic pain may result from disorders of the peripheral nervous system or the central nervous system (brain and spinal cord). Thus, neuropathic pain may be divided into peripheral neuropathic pain, central neuropathic pain, or mixed (peripheral and central) neuropathic pain.

Central neuropathic pain is found in spinal cord injury, multiple sclerosis, and some strokes. Fibromyalgia, a disorder of chronic widespread pain, is potentially a central pain disorder and is responsive to medications that are effective for neuropathic pain.

Aside from diabetes and other metabolic conditions, the common causes of painful peripheral neuropathies are herpes zoster infection, HIV-related neuropathies, nutritional deficiencies, toxins, remote manifestations of malignancies, genetic, and immune mediated disorders or physical trauma to a nerve trunk.

Neuropathic pain is common in cancer as a direct result of cancer on peripheral nerves (e.g., compression by a tumor), or as a side effect of chemotherapy, radiation injury or surgery.

Mechanisms

The starting point for neuropathic pain is a lesion or dysfunction within the somatosensory system. Current knowledge regarding the mechanisms of neuropathic pain is incomplete and is biased by a focus on animal models of peripheral nerve injury.

Peripheral

Under normal circumstances, pain sensations are carried by unmyelinated and thinly myelinated nerve fibers, designated C-fibers and A-delta fibers, respectively. After a peripheral nerve lesion, aberrant regeneration may occur. Neurons become unusually sensitive and develop spontaneous pathological activity, abnormal excitability, and heightened sensitivity to chemical, thermal and mechanical stimuli. This phenomenon is called "peripheral sensitization".

Central

The dorsal horn neurons give rise to the spinothalamic tract (STT), which constitutes the major ascending nociceptive pathway. As a consequence of ongoing spontaneous activity arising in the periphery, STT neurons develop an increased background activity, enlarged receptive field and increased responses to afferent impulses, including normally innocuous tactile stimuli. This phenomenon is called central sensitization. Central sensitization has been proposed as an important mechanism of persistent neuropathic pain.

Other mechanisms, however, may take place at the central level after peripheral nerve damage. The loss of afferent signals induces functional changes in dorsal horn neurons. A decrease in the large fiber input decreases activity of interneurons inhibiting nociceptive neurons i.e. loss of afferent inhibition. Hypoactivity of the descending antinociceptive systems or loss of descending inhibition may be another factor. With loss of neuronal input (deafferentation) the STT neurons begin to fire spontaneously, a phenomenon designated "deafferentation hypersensitivity."

Non-neural glial cells may play a role in central sensitization. Peripheral nerve injury induces glial to releasing glial proinflammatory cytokines and glutamate which, in turn influence neurons.

Mechanisms at light-microscopic and submicroscopic levels

The phenomenon described above are dependent on changes at light-microscopic and submicroscopic levels. Altered expression of ion channels, changes in neurotransmitters and their receptors as well as altered gene expression in response to neural input are at play.

Treatments

Neuropathic pain can be very difficult to treat with only some 40-60% of patients achieving partial relief.

In addition to the work of Dworkin, O'Connor and Backonja et al., cited above, there have been several recent attempts to derive guidelines for pharmacological therapy. These have combined evidence from randomized controlled trials with expert opinion.

Determining the best treatment for individual patients remains challenging. Attempts to translate scientific studies into best practices are limited by factors such as differences in reference populations and a lack of head-to-head studies. Furthermore, multi-drug combinations and the needs of special populations, such as children, require more study.

It is common practice in medicine to designate classes of medication according to their most common or familiar use e.g. as "antidepressants" and "anti-epileptic drugs" (AED's). These drugs have alternate uses to treat pain because the human nervous system employs common mechanisms for different functions, for example ion channels for impulse generation and neurotransmitters for cell-to-cell signaling.

Favored treatments are certain antidepressants e.g. tricyclics and selective serotonin-norepinephrine reuptake inhibitors (SNRI's), anticonvulsants, especially pregabalin (Lyrica) and gabapentin (Neurontin), and topical lidocaine. Opioid analgesics and tramadol are recognized as useful agents but are not recommended as first line treatments. Many of the pharmacologic treatments for chronic neuropathic pain decrease the sensitivity of nociceptive receptors, or desensitize C fibers such that they transmit fewer signals.

Some drugs may exert their influence through descending pain modulating pathways. These descending pain modulating pathways originate in the brainstem.

Antidepressants

The functioning of antidepressants is different in neuropathic pain from that observed in depression. Activation of descending norepinephrinergic and serotonergic pathways to the spinal cord limit pain signals ascending to the brain. Antidepressants will relieve neuropathic pain in non-depressed persons.

In animal models of neuropathic pain it has been found that compounds which only block serotonin reuptake do not improve neuropathic pain. Similarly, compounds that only block norepinephrine reuptake also do not improve neuropathic pain. Dual serotonin-norepinephrine reuptake inhibitors such as duloxetine, venlafaxine, and milnacipran, as well as tricyclic antidepressants such as nortriptyline and desipramine improve neuropathic pain and are considered first-line medications for this condition.

Bupropion has been found to have efficacy in the treatment of neuropathic pain.

Tricyclic antidepressants may also have effects on sodium channels.

Anticonvulsants

Pregabalin (Lyrica) and gabapentin (Neurontin) work by blocking specific calcium channels on neurons and are preferred first-line medications for diabetic neuropathy. The actions of the anticonvulsants carbamazepine (Tegretol) and oxcarbazepine (Trileptal) are especially effective on trigeminal neuralgia, are principally on sodium channels.

Lamotrigine may have a special role in treating two conditions for which there are few alternatives, namely post stroke pain and HIV/AIDS-related neuropathy caused by antiretroviral therapy.

Opioids

Opioids, also known as narcotics, are increasingly recognized as important treatment options for chronic pain. They are not considered first line treatments in neuropathic pain but remain the most consistently effective class of drugs for this condition. Opioids must be used only in appropriate individuals and under close medical supervision.

Several opioids, particularly methadone, have NMDA antagonist activity in addition to their μ-opioid agonist properties.

Methadone and ketobemidone possess NMDA antagonism. Methadone does so because it is a racemic mixture; only the l-isomer is a potent μ-opioid agonist. The d-isomer does not have opioid agonist action and acts as an NMDA antagonist; d-methadone is analgesic in experimental models of chronic pain. . Clinical studies are in progress to test the efficacy of d-methadone in neuropathic pain syndromes.

There is little evidence to indicate that one strong opioid is more effective than another. Expert opinion leans toward the use of methadone for neuropathic pain, in part because of its NMDA antagonism. It is reasonable to base the choice of opioid on other factors.

Topical agents

In some forms of neuropathy, especially post-herpetic neuralgia, the topical application of local anesthetics such as lidocaine can provide relief. A transdermal patch containing lidocaine is available commercially in some countries.

Repeated topical applications of capsaicin, are followed by a prolonged period of reduced skin sensibility referred to as desensitization, or nociceptor inactivation. Capsaicin not only depletes substance P but also results in a reversible degeneration of epidermal nerve fibers. Nevertheless, benefits appear to be modest with standard (low) strength preparations.

Cannabinoids

Marijuana's active ingredients are called cannabinoids. Unfortunately, strongly held beliefs make discussion of the appropriate use of these substances, in a medical context, difficult. Similar considerations apply to opioids.

A recent study showed smoked marijuana is beneficial in treating symptoms of HIV-associated peripheral neuropathy. Nabilone is an artificial cannabinoid which is significantly more potent than delta-9-tetrahydrocannabinol (THC). Nabilone produces

less relief of chronic neuropathic pain and had slightly more side effects than dihydrocodeine.

The predominant adverse effects are CNS depression and cardiovascular effects which are mild and well tolerated but, psychoactive side effects limit their use. A complicating issue may be a narrow therapeutic window; lower doses decrease pain but higher doses have the opposite effect.

Sativex, a fixed dose combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol, is sold as an oromucosal spray. The product is approved in Canada as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis, and for cancer related pain.

Long-term studies are needed to assess the probability of weight gain, unwanted psychological influences and other adverse effects.

Botulinum Toxin Type A (Botox, BTX-A)

Botulinum Toxin Type A (BTX-A) is best know by its trade name, Botox. Local intradermal injection of BTX-A is helpful in chronic focal painful neuropathies. The analgesic effects are not dependent on changes in muscle tone. Benefits persist for at least 14 weeks from the time of administration.

The utility of BTX-A in other painful conditions remains to be established.

NMDA antagonism

The *N*-methyl-D-aspartate (NMDA) receptor seems to play a major role in neuropathic pain and in the development of opioid tolerance. Dextromethorphan is an NMDA antagonist at high doses. Experiments in both animals and humans have established that NMDA antagonists such as ketamine and dextromethorphan can alleviate neuropathic pain and reverse opioid tolerance. Unfortunately, only a few NMDA antagonists are clinically available and their use is limited by a very short half life (dextrometorphan), weak activity (memantine)or unacceptable side effects (ketamine).

Reducing sympathetic nervous stimulation

In some neuropathic pain syndromes, "crosstalk" occurs between descending sympathetic nerves and ascending sensory nerves. Increases in sympathetic nervous system activity result in an increase of pain; this is known as sympathetically-mediated pain.

Lesioning operations on the sympathetic branch of the autonomic nervous system are sometimes carried out.

There are methods of treating sympathetically maintained pain in peripheral tissues. This is done topically to a patient having sympathetically maintained pain at a peripheral site

where the pain originates. Wherein the sympathetically maintained pain can be diagnosed by local anesthetic blockade of the appropriate sympathetic ganglion or adrenergic receptor blockade via intravenous administration of Phentolamine, and rekindled by intradermal injection of Norepinephrine.

Dietary supplements

There are two dietary supplements that have clinical evidence showing them to be effective treatments of diabetic neuropathy; alpha lipoic acid and benfotiamine.

A 2007 review of studies found that injected (parenteral) administration of alpha lipoic acid (ALA) was found to reduce the various symptoms of peripheral diabetic neuropathy. While some studies on orally administered ALA had suggested a reduction in both the positive symptoms of diabetic neuropathy (including stabbing and burning pain) as well as neuropathic deficits (paresthesia), the metanalysis showed "more conflicting data whether it improves sensory symptoms or just neuropathic deficits alone". There is some limited evidence that ALA is also helpful in some other non-diabetic neuropathies.

Benfotiamine is a lipid-soluble form of thiamine that has several placebo-controlled double-blind trials proving efficacy in treating neuropathy and various other diabetic comorbidities.

Other modalities

In addition to pharmacological treatment several other modalities are commonly recommended. While lacking adequate double blind trials, these have shown to reduce pain and improve patient quality of life for chronic neuropathic pain: chiropractic, yoga, massage, meditation, cognitive therapy, and prescribed exercise. Some pain management specialists will try acupuncture, with variable results.

Transcutaneous electrical nerve stimulation (TENS) may be worth considering in chronic neurogenic pain. TENS, with certain electrical waveforms, appears to have an acupuncture-like function.

Infrared photo therapy has been used to treat neuropathic symptoms. However, recent work has cast doubt on the value of this approach.

Neuromodulators

Neuromodulation is a field of science, medicine and bioengineering that encompasses both implantable and non-implantable technologies (electrical and chemical) for treatment purposes.

Implanted devices are expensive and carry the risk of complications. Available studies have focused on conditions having a different prevalence than neuropathic pain patients

in general. More research is needed to define the range of conditions for which they might be beneficial.

Spinal cord stimulators and implanted spinal pumps

Spinal cord stimulators, use electrodes placed adjacent to, but outside the spinal cord. The overall complication rate is one-third, most commonly due to lead migration or breakage. Lack of pain relief sometimes prompts device removal.

Infusion pumps deliver medication directly to the fluid filled (subarachnoid) space surrounding the spinal cord. Opioids alone or opioids with adjunctive medication (either a local anesthetic or clonidine) or more recently ziconotide are infused. Complications such as, serious infection (meningitis), urinary retention, hormonal disturbance and intrathecal granuloma formation have been noted.

There are no randomized studies of infusion pumps. For selected patients 50% or greater pain relief is achieved in 38% to 56% at six months but declines with the passage of time. These results must be viewed skeptically since placebo effects cannot be evaluated.

Motor cortex stimulation

Stimulation of the primary motor cortex through electrodes placed within the skull but outside the thick meningeal membrane (dura) has been used to treat pain. The level of stimulation is below that for motor stimulation. As compared with spinal stimulation, which requires a noticeable tingling (paresthesia) for benefit, the only palpable effect is pain relief.

Deep brain stimulation

The best long-term results with deep brain stimulation have been reported with targets in the periventricular/periaqueductal grey matter (79%), or the periventricular/periaqueductal grey matter plus thalamus and/or internal capsule (87%). There is a significant complication rate which increase over time.

Chapter 11

Phantom Pain

Phantom pain	
ICD-9	353.6
DiseasesDB	29431

Phantom pain sensations are described as perceptions that an individual experiences relating to a limb or an organ that is not physically part of the body. Limb loss is a result of either removal by amputation or congenital limb deficiency (Giummarra et al., 2007). However, phantom limb sensations can also occur following nerve avulsion or spinal cord injury. Sensations are recorded most frequently following the amputation of an arm or a leg, but may also occur following the removal of a breast or an internal organ. Phantom limb pain is the feeling of pain in an absent limb or a portion of a limb. The pain sensation varies from individual to individual.

Phantom limb sensation is the term given to any sensory phenomenon (except pain) which is felt at an absent limb or a portion of the limb. It has been known that at least 80% of amputees experience phantom sensations at some time of their lives. Some experience some level of this phantom pain and feeling in the missing limb for the rest of their lives.

There are various types of sensations that may be felt:

- Sensations related to the phantom limb's posture, length and volume e.g. feeling that the phantom limb is behaving just like a normal limb like sitting with the knee bent or feeling that the phantom limb is as heavy as the other limb. Sometimes, an amputee will experience a sensation called telescoping. This is the feeling that the phantom limb is gradually shortening over time.
- Sensations of movement (e.g. feeling that the phantom foot is moving).
- Sensations of touch, temperature, pressure and itchiness. Many amputees report of feeling heat, tingling, itchiness, and pain.

The term “phantom limb” was first coined by American neurologist Silas Weir Mitchell in 1871 (Halligan, 2002). Mitchell described that “thousands of spirit limbs were haunting as many good soldiers, every now and then tormenting them” (Bittar et al.,

2005). However, in 1551, French military surgeon Ambroise Paré recorded the first documentation of phantom limb pain when he reported that, “For the patients, long after the amputation is made, say that they still feel pain in the amputated part” (Bittar et al., 2005).

Signs and symptoms

Phantom pain involves the sensation of pain in a part of the body that has been removed.

Epidemiology

Phantom limb pain and phantom limb sensations are linked, but must be differentiated from one another. While phantom limb sensations are experienced by those with congenital limb deficiency, spinal cord injury, and amputation, phantom limb pain occurs almost exclusively as a result of amputation (Kooijman et al., 2000). Almost immediately following the amputation of a limb, 90-98% of patients report experiencing a phantom sensation. Nearly 75% of individuals experience the phantom as soon as anesthesia wears off, and the remaining 25% of patients experience phantoms within a few days or weeks (Ramachandran and Herstein, 1998). Of those experiencing innocuous sensations, a majority of patients also report distinct painful sensations.

The prevalence of phantom limb pain differs based on the location of the amputation. The prevalence of phantom pain in upper limb amputees is nearly 82%, while the prevalence of pain in lower limb amputees is only 54% (Kooijman et al., 2000). Age and gender have not been shown to affect the onset or duration of phantom limb pain. Although it has not been fully explored, one investigation of lower limb amputation observed that as stump length decreased, there was a greater incidence of moderate and severe phantom pain (Bittar et al., 2005).

Pathophysiology

The neurological basis and mechanisms for phantom limb pain are all derived from experimental theories and observations. Little is known about the true mechanism causing phantom pains, and many theories highly overlap. Historically, phantom pains were thought to originate from neuromas located at the stump tip. Traumatic neuromas, or non-tumor nerve injuries, often arise from surgeries and result from the abnormal growth of injured nerve fibers. Although stump neuromas contribute to phantom pains, they are not the sole cause. This is because patients with congenital limb deficiency can sometimes, although rarely, experience phantom pains. This suggests that there is a central representation of the limb responsible for painful sensations (Ramachandran and Herstein, 1998). Currently, theories are based on altered neurological pathways and cortical reorganization. Although they are highly intertwined, mechanisms are often separated into peripheral, spinal, and central mechanisms.

Peripheral mechanisms

Neuromas formed from injured nerve endings at the stump site are able to fire abnormal action potentials, and were historically thought to be the main cause of phantom limb pain. Although neuromas are able to contribute to phantom pain, pain is not completely eliminated when peripheral nerves are treated with conduction blocking agents (Ramachandran and Herstein, 1998). Physical stimulation of neuromas can increase C fiber activity, thus increasing phantom pain, but pain still persists once the neuromas have ceased firing action potentials. The peripheral nervous system is thought to have at most a modulation effect on phantom limb pain (Bitter et al., 2005)

Spinal mechanisms

In addition to peripheral mechanisms, spinal mechanisms are thought to have an influencing role in phantom pains. Peripheral nerve injury can lead to the degeneration of C fibers in the dorsal horn of the spinal cord, and terminating A fibers may subsequently branch into the same lamina (Bittar et al., 2005). If this occurs, A fiber inputs could be reported as noxious stimuli. Substance P, involved in the transmission of pain signals, is usually expressed by Aδ and C fibers, but following peripheral nerve damage, substance P is expressed by Aβ fibers (Bittar et al., 2005). This leads to hyperexcitability of the spinal cord, which usually occurs only in the presence of noxious stimuli. Because patients with complete spinal cord injury have experienced phantom pains, there must be an underlying central mechanism responsible for the generation of phantom pains.

Central mechanisms and cortical remapping

Under ordinary circumstances, the genetically determined circuitry in the brain remains largely stable throughout life. It was thought, until about 30 years ago, that no new neural circuits could be formed in the adult mammalian brain (Ramachandran and Hirstein, 1998). Recently, functional MRI studies in amputees have shown that almost all patients have experienced motor cortical remapping (Cruz et al., 2003). The majority of motor reorganization has occurred as a downward shift of the hand area of the cortex onto the area of face representation, especially the lips. Sometimes there is a side shift of the hand motor cortex to the ipsilateral cortex (Cruz et al., 2003). In patients with phantom limb pain, the reorganization was great enough to cause a change in cortical lip representation into the hand areas only during lip movements (Cruz et al., 2003). It has also been found that there is a high correlation between the magnitude of phantom limb pain and the extent to which the shift of the cortical representation of the mouth into the hand area in motor and somatosensory cortical reorganization has occurred (Karl et al., 2001). Additionally, as phantom pains in upper extremity amputees increased, there was a higher degree of medial shift of the facial motor representation (Karl et al., 2001). There are Multiple theories that try to explain how cortical remapping occurs in amputees, but none have been supported to a great extent.

The neuromatrix

The neuromatrix theory proposes that there is an extensive network connecting the thalamus and the cortex, and the cortex and the limbic system (Bittar et al., 2005). It is a theory that extends beyond body schema theory and incorporates the conscious awareness of oneself. This theory proposes that conscious awareness and the perception of self are generated in the brain via patterns of input that can be modified by different perceptual inputs (Giummarra et al., 2007). The network is genetically predetermined, and is modified throughout one's lifetime by various sensory inputs to create a neurosignature. It is the neurosignature of a specific body part that determines how it is consciously perceived (Bittar et al., 2005). The input systems contributing to the neurosignature are primarily the somatosensory, limbic, and thalamocortical systems. The neuromatrix theory aims to explain how certain activities associated with pain lead to the conscious perception of phantom pain. The persistence of the neurosignature, even after limb amputation, may be the cause of phantom sensations and pain. Phantom pain may arise from abnormal reorganization in the neuromatrix to a pre-existing pain state (Melzack, 1992).

Opposition to the neuromatrix theory exists largely because it fails to explain why relief from phantom sensations rarely eliminates phantom pains. It also does not address how sensations can spontaneously end and how some amputees do not experience phantom sensations at all (Bittar et al., 2005). In addition, a major limitation of the neuromatrix theory is that it too broadly accounts for various aspects of phantom limb perception. It is also likely that it is too difficult to be tested empirically, especially when testing painless phantom sensations (Giummarra et al., 2007).

Management

Various methods have been used to treat phantom limb pain. Doctors may prescribe medications to reduce the pain. Some antidepressants or antiepileptics have been shown to have a beneficial effect on reducing phantom limb pain. Often physical methods such as light massage, electrical stimulation, and hot and cold therapy have been used with variable results.

There are many different treatment options for phantom limb pain that are actively being researched. Most treatments do not take into account the mechanisms underlying phantom pains, and are therefore ineffective. However, there are a few treatment options that have been shown to alleviate pain in some patients, but these treatment options usually have a success rate less than 30% (Bittar et al., 2005). It is important to note that this rate of success does not exceed the placebo effect. It is also important to note that because the degree of cortical reorganization is proportional to phantom limb pains, any perturbations to the amputated regions may increase pain perception (Bittar et al., 2005).

Non surgical techniques

Mirror box therapy

Mirror box therapy allows for illusions of movement and touch in a phantom limb by inducing somatosensory and motor pathway coupling between the phantom and real limb (Giummarra et al., 2007). Many patients experience pain as a result of a clenched phantom limb, and because phantom limbs are not under voluntary control, unclenching becomes impossible (Ramachandran and Rogers-Ramachandran, 1996). The theory behind the mirror box treatment is that the brain has become accustomed to the fact that a phantom limb is paralyzed because there is no feedback from the phantom back to the brain to inform it otherwise. Ramachandran and Rogers-Ramachandran believed that if the brain received visual feedback that the limb had moved, then the phantom limb would become unparalyzed (Ramachandran and Rogers-Ramachandran, 1996).

To create the visual feedback, mirror boxes are constructed to create an illusion of a second limb. The mirror box is constructed so that it has a vertical mirror placed in the center, and the lid remains off. The intact limb is placed on one side of the mirror, and in the patient's sight, while the amputated limb is placed on the other side, out of sight. The patient sees an intact second limb through the mirror and sends motor commands to both limbs to make symmetric movements. The movement gives the brain positive feedback that the phantom has moved, and it becomes unparalyzed (Ramachandran and Rogers-Ramachandran, 1996).

In a study of ten patients with upper phantom limb paralysis, nine patients were able to move the phantom limb, and eight of the patients able to move the phantom limb had their pain alleviated (Ramachandran and Rogers-Ramachandran, 1996). Since Ramachandran and Ramachandran's pioneer study, there have been multiple additional studies to support the mirror box findings for patients with upper limb phantom pain. MacLachlan, McDonald, and Walcoch presented the first case of mirror box treatment for lower limb phantoms in 2004. The patient, Alan, experienced a painful crossing of his toes in the morning, and the pain worsened as the day progressed. After three weeks of mirror box treatment twice a day, Alan no longer felt any painful sensations from crossed toes (MacLachlan, McDonald, and Walcoch, 2004).

Pharmacological treatment

Pharmacological techniques are often continued in conjunction with other treatment options. Doses or pain medications needed often drop substantially when combined with other techniques, but rarely are discontinued completely. Tricyclic antidepressants, such as amitriptyline, and sodium channel blockers, mainly carbamazepine, are often used to relieve chronic pain, and recently have been used in an attempt to reduce phantom pains. Pain relief may also be achieved through use of opioids, ketamine, calcitonin, and lidocaine (Bittar et al., 2005).

Surgical techniques

Deep-brain stimulation

Deep brain stimulation is a surgical technique used to alleviate patients from phantom limb pain. Prior to surgery, patients undergo functional brain imaging techniques such as PET scans and functional MRI to determine an appropriate trajectory of where pain is originating. Surgery is then carried out under local anesthetic, because patient feedback during the operation is needed. In the study conducted by Bittar et al., a radiofrequency electrode with four contact points was placed on the brain. Once the electrode was in place, the contact locations were altered slightly according to where the patient felt the greatest relief from pain. Once the location of maximal relief was determined, the electrode was implanted and secured to the skull. After the primary surgery, a secondary surgery under general anesthesia was conducted. A subcutaneous pulse generator was implanted into a pectoral pocket below the clavicle to stimulate the electrode (Bittar et al., 2005). It was found that all three patients studied had gained satisfactory pain relief from the deep brain stimulation. Pain had not been completely eliminated, but the intensity had been reduced by over 50% and the burning component had completely vanished (Bittar et al., 2005).

Chapter 12

Pain Management

Pain management (also called pain medicine; algiatry) is a branch of medicine employing an interdisciplinary approach for easing the suffering and improving the quality of life of those living with pain. The typical pain management team includes medical practitioners, clinical psychologists, physiotherapists, occupational therapists, and nurse practitioners. Pain sometimes resolves promptly once the underlying trauma or pathology has healed, and is treated by one practitioner, with drugs such as analgesics and (occasionally) anxiolytics. Effective management of long term pain, however, frequently requires the coordinated efforts of the management team.

Medicine treats injury and pathology to support and speed healing; and treats distressing symptoms such as pain to relieve suffering during treatment and healing. When a painful injury or pathology is resistant to treatment and persists, when pain persists after the injury or pathology has healed, and when medical science cannot identify the cause of pain, the task of medicine is to relieve suffering. Treatment approaches to long term pain include pharmacologic measures, such as analgesics, tricyclic antidepressants and anticonvulsants, interventional procedures, physical therapy, physical exercise, application of ice and/or heat, and psychological measures, such as biofeedback and cognitive behavioral therapy.

Medical specialties

Pain management practitioners come from all fields of medicine. Most often, pain fellowship trained physicians are anesthesiologists, neurologists, physiatrists or psychiatrists. Palliative care doctors are also specialists in pain management. Some practitioners have not been fellowship trained and have opted for certification by the American Board of Pain Medicine which is not recognized by the American Board of Medical Specialties and does not indicate fellowship training. However, the American Board of Anesthesiology and the American Board of Physical Medicine and Rehabilitation have a subspecialty in pain management which is recognized by the American Board of Medical Specialties and does indicate fellowship training. Some practitioners focus more on the pharmacologic management of the patient, while others are very proficient at the interventional management of pain. Interventional procedures - typically used for chronic back pain - include: epidural steroid injections, facet joint injections, neurolytic blocks, spinal cord stimulators and intrathecal drug delivery system

implants. Over the last several years the number of interventional procedures done for pain has grown.

As well as medical practitioners, the area of pain management may often benefit from the input of physiotherapists, chiropractors, clinical psychologists and occupational therapists, amongst others. Together the multidisciplinary team can help create a package of care suitable to the patient.

Because of the fast growth in the field of pain medicine many practitioners have entered the field, with many of these practitioners being not board certified or being certified by unrecognized boards.

Medications

The World Health Organization (WHO) recommends a *pain ladder* for managing analgesia. It was first described for use in cancer pain, but it can be used by medical professionals as a general principle when dealing with analgesia for any type of pain. In the treatment of chronic pain, whether due to malignant or benign processes, the three-step WHO Analgesic Ladder provides guidelines for selecting the kind and stepping up the amount of analgesia. The exact medications recommended will vary with the country and the individual treatment center, but the following gives an example of the WHO approach to treating chronic pain with medications. If, at any point, treatment fails to provide adequate pain relief, then the doctor and patient move onto the next step.

Mild pain

Paracetamol (acetaminophen), or a non steroidal anti-inflammatory drug such as ibuprofen.

Mild to moderate pain

Paracetamol, an NSAID and/or paracetamol in a combination product with a weak opioid such as hydrocodone used in combination, may provide greater relief than their separate use.

Moderate to severe pain

When treating moderate to severe pain, the type of the pain, acute or chronic, needs to be considered. The type of pain can result in different medications being prescribed. Certain medications may work better for acute pain, others for chronic pain, and some may work equally well on both. Acute pain medication is for rapid onset of pain such as from an inflicted trauma or to treat post-operative pain. Chronic pain medication is for alleviating long-lasting, ongoing pain.

Morphine is the gold standard to which all narcotics are compared. Fentanyl has the benefit of less histamine release and thus fewer side effects. It can also be administered

via transdermal patch which is convenient for chronic pain management. Oxycodone is used across the Americas and Europe for relief of serious chronic pain; its main slow-release formula is known as OxyContin, and short-acting tablets, capsules, syrups and ampoules are available making it suitable for acute intractable pain or breakthrough pain. Diamorphine, methadone and buprenorphine are used less frequently. Pethidine, known in North America as meperidine, is not recommended for pain management due to its low potency, short duration of action, and toxicity associated with repeated use. Pentazocine, dextromoramide and dipipanone are also not recommended in new patients except for acute pain where other analgesics are not tolerated or are inappropriate, for pharmacological and misuse-related reasons. Amitriptyline is prescribed for chronic muscular pain in the arms, legs, neck and lower back. While opiates are often used in the management of chronic pain, high doses are associated with an increased risk of opioid overdose.

Opioids

Opioid medications can provide a short, intermediate or long acting analgesia depending upon the specific properties of the medication and whether it is formulated as an extended release drug. Opioid medications may be administered orally, by injection, via nasal mucosa or oral mucosa, rectally, transdermally, intravenously, epidurally and intrathecally. In chronic pain conditions that are opioid responsive a combination of a long-acting or extended release medication is often prescribed in conjunction with a shorter-acting medication for breakthrough pain, or exacerbations.

Most opioid treatment is oral (tablet, capsule or liquid), but suppositories and skin patches can be prescribed. An opioid injection is rarely needed for patients with chronic pain.

Although opioids are strong analgesics, they do not provide complete analgesia regardless of whether the pain is acute or chronic in origin. Opioids are efficacious analgesics in chronic malignant pain and modestly effective in nonmalignant pain management. However, there are associated adverse effects, especially during the commencement or change in dose. When opioids are used for prolonged periods drug tolerance, chemical dependency, diversion and addiction may occur.

Clinical guidelines for prescribing opioids for chronic pain have been issued by the American Pain Society and the American Academy of Pain Medicine. Included in these guidelines is the importance of assessing the patient for the risk of substance abuse, misuse, or addiction; a personal or family history of substance abuse is the strongest predictor of aberrant drug-taking behavior. Physicians who prescribe opioids should integrate this treatment with any psychotherapeutic intervention the patient may be receiving. The guidelines also recommend monitoring not only the pain but also the level of functioning and the achievement of therapeutic goals. The prescribing physician should be suspicious of abuse when a patient reports a reduction in pain but has no accompanying improvement in function or progress in achieving identified goals.

Non-steroidal anti-inflammatory drugs

The other major group of analgesics are non-steroidal anti-inflammatory drugs (NSAID). Acetaminophen is not always included in this class of medications. However, acetaminophen may be administered as a single medication or in combination with other analgesics (both NSAIDs and opioids). The alternatively prescribed NSAIDs such as ketoprofen and piroxicam, have limited benefit in chronic pain disorders and with long-term use is associated with significant adverse effects. The use of selective NSAIDs designated as selective COX-2 inhibitors have significant cardiovascular and cerebrovascular risks which have limited their utilization.

Antidepressants and antiepileptic drugs

Some antidepressant and antiepileptic drugs are used in chronic pain management and act primarily within the pain pathways of the central nervous system, though peripheral mechanisms have been attributed as well. These mechanisms vary and in general are more effective in neuropathic pain disorders as well as complex regional pain syndrome. Drugs such as gabapentin have been widely prescribed for the off-label use of pain control. The list of side effects for these classes of drugs are typically much longer than opiate or NSAID treatments for chronic pain, and many antiepileptics cannot be suddenly stopped without the risk of seizure.

Other analgesics

Other drugs are often used to help analgesics combat various types of pain and parts of the overall pain experience. In addition to gabapentin, the vast majority of which is used off-label for this purpose, orphenadrine, cyclobenzaprine, trazodone and other drugs with anticholinergic properties are useful in conjunction with opioids for neuropathic pain. Orphenadrine and cyclobenzaprine are also muscle relaxants and are therefore particularly useful in painful musculoskeletal conditions. Clonidine has found use as an analgesic for this same purpose and all of the mentioned drugs potentiate the effects of opioids overall.

Procedures

Pulsed radiofrequency, neuromodulation, direct introduction of medication and nerve ablation may be used to target either the tissue structures and organ/systems responsible for persistent nociception or the nociceptors from the structures implicated as the source of chronic pain.

An intrathecal pump used to deliver very small quantities of medications directly to the spinal fluid. This is similar to epidural infusions used in labour and postoperatively. The major differences are that it is much more common for the drug to be delivered into the spinal fluid (intrathecal) rather than epidurally, and the pump can be fully implanted under the skin. This approach allows a higher dose of the drug to be delivered directly to the site of action, with fewer systemic side effects.

A spinal cord stimulator is an implantable medical device that creates electric impulses and applies them near the dorsal surface of the spinal cord provides a paresthesia ("tingling") sensation that alters the perception of pain by the patient.

Physical approach

Physiatry

Physical medicine and rehabilitation (physiatry) employs diverse physical techniques such as thermal agents and electrotherapy, as well as therapeutic exercise and behavioral therapy, alone or in tandem with interventional techniques and conventional pharmacotherapy to treat pain, usually as part of an interdisciplinary or multidisciplinary program.

TENS

Transcutaneous electrical nerve stimulation has been found to be ineffective for lower back pain, however, it might help with diabetic neuropathy.

Acupuncture

Acupuncture involves the insertion and manipulation of needles into specific points on the body to relieve pain or for therapeutic purposes. In 2003, the World Health Organization published an article synthesizing the scientific research (controlled trials) of the time, and concluded acupuncture is helpful for the treatment of pain in some cases of acute pain in the epigastric area, facial pain, headache, knee pain, low back pain, neck pain, pain in dentistry, postoperative pain, renal colic, and sciatica. The authors also concluded acupuncture has demonstrated effectiveness in other conditions for which further proof is needed. This review has been criticized for giving too much weight to low-quality clinical trials, and including a large number of trials originating in China. The latter issue is considered problematic because trials originating in the West include a mixture of positive, negative and neutral results while all trials in China are positive (attributed to publication bias rather than fraud). An analysis of the 13 highest quality studies of pain treatment with acupuncture, published in January 2009 in the *British Medical Journal*, concluded there was little difference in the effect of real, sham and no acupuncture. There is general agreement that acupuncture is safe when administered by well-trained practitioners using sterile needles, and that further research is appropriate.

LLLT

A 2007 review concluded low level laser therapy may be effective in reducing inflammation and pain, while a 2008 Cochrane collaboration review concluded that there was insufficient evidence to support the use of LLLT in the management of low back pain.

Psychological approach

Cognitive and behavioral therapy

Mindfulness-based cognitive therapy, the use of stress reduction and relaxation, has been found to reduce chronic pain in some patients. Applied behavior analysis views chronic pain as a consequence of both respondent and operant conditioning, where a patient learns to display pain behavior in the presence of specific environmental antecedents and consequences. The model was first proposed by Fordyce in 1976. The behavioral model has shown effectiveness in reducing pain responses though operant based interventions. Though cognitive-behavioral intervention can be an effective and economical means of treating chronic pain, the effects are rather modest and a substantial portion of patients gain no benefit.

Biofeedback

Biofeedback based on behavioral principles has shown some success for chronic pain, demonstrating greater improvement in one study than peers undergoing cognitive-behavioral therapy and conservative medical treatment, though a different study showed improvements over wait-list controls but no difference between biofeedback and cognitive-behavioral therapy.

Hypnosis

A 2007 review of 13 studies found evidence for the efficacy of hypnosis in the reduction of pain in some conditions, though the number of patients enrolled in the studies was small, bringing up issues of power to detect group differences, and most lacked credible controls for placebo and/or expectation. The authors concluded that "although the findings provide support for the general applicability of hypnosis in the treatment of chronic pain, considerably more research will be needed to fully determine the effects of hypnosis for different chronic-pain conditions." (p. 283)

Under-treatment

Inadequate treatment of pain is widespread throughout surgical wards, intensive care units, accident and emergency departments, in general practice, in the management of all forms of chronic pain including cancer pain, and in end of life care. This neglect is extended to all ages, from neonates to the frail elderly. In September 2008, the World Health Organization (WHO) estimated that approximately 80 percent of the world population has either no or insufficient access to treatment for moderate to severe pain. Every year tens of millions of people around the world, including around four million cancer patients and 0.8 million HIV/AIDS patients at the end of their lives suffer from such pain without treatment. Yet the medications to treat pain are cheap, safe, effective, generally straightforward to administer, and international law obliges countries to make adequate pain medications available.

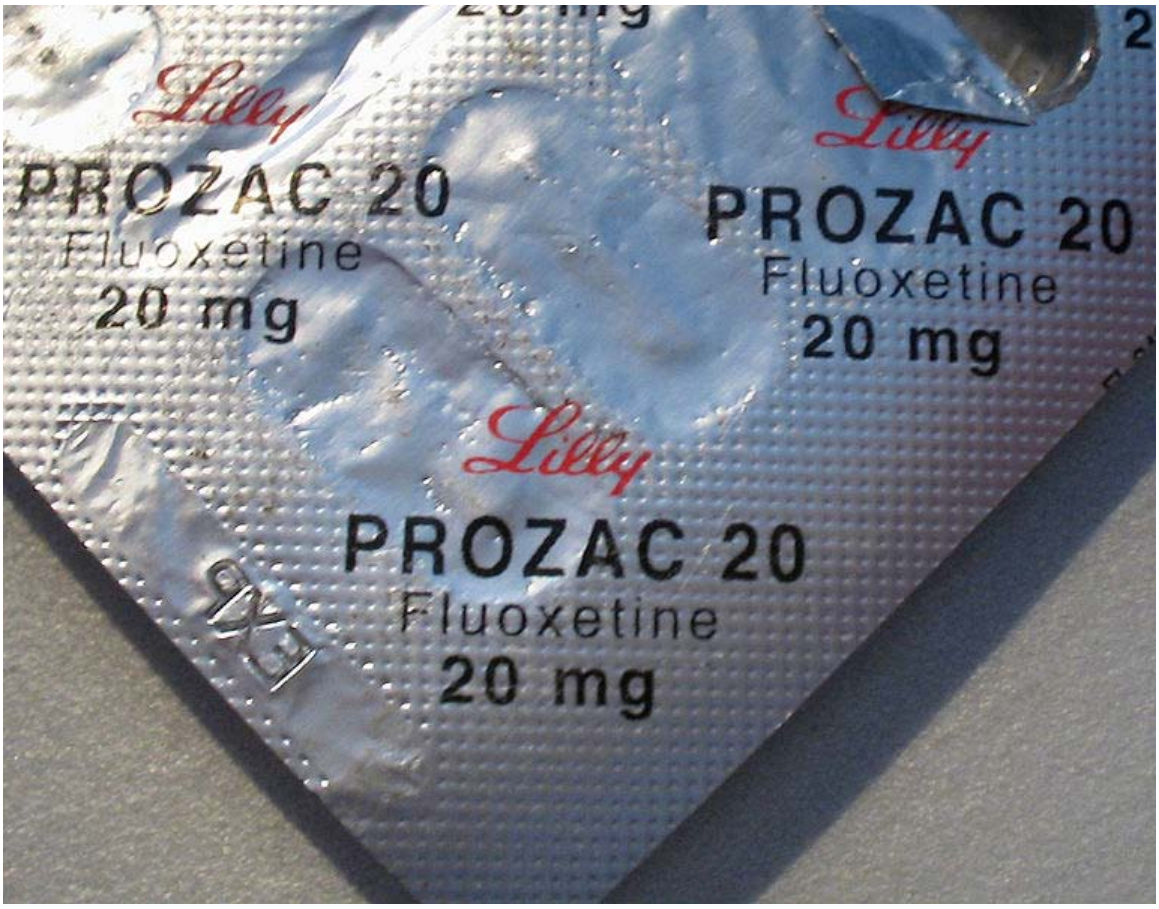
Reasons for deficiencies in pain management include cultural, societal, religious, and political attitudes, including acceptance of torture. Moreover, the biomedical model of disease, focused on pathophysiology rather than quality of life, reinforces entrenched attitudes that marginalize pain management as a priority. Other reasons may have to do with inadequate training, personal biases or fear of prescription drug abuse.

In the United States, Hispanic and African Americans are more likely to suffer needlessly in the hands of a physician than whites; and women's pain is more likely to be undertreated than men's. It is often recognized that a great number of patients suffering from chronic pain are being under-treated because physicians fail to provide comprehensive pain treatment. This failure may be due to physicians' fear of being accused of over-prescribing, despite the relative rarity of prosecutions (147 cases across USA in 2006), or physicians' poor understanding of the health risks attached to opioid prescription. As a result of two recent cases in California though, where physicians who failed to provide adequate pain relief were successfully sued for elder abuse, the North American medical and health care communities appear to be undergoing a shift in perspective. The California Medical Board publicly reprimanded the physician in the second case; the federal Center for Medicare and Medicaid Services has declared a willingness to charge with fraud health care providers who accept payment for providing adequate pain relief while failing to do so; and clinical practice guidelines and standards are evolving into clear, unambiguous statements on acceptable pain management, so health care providers, in California at least, can no longer avoid culpability by claiming that poor or no pain relief meets community standards.

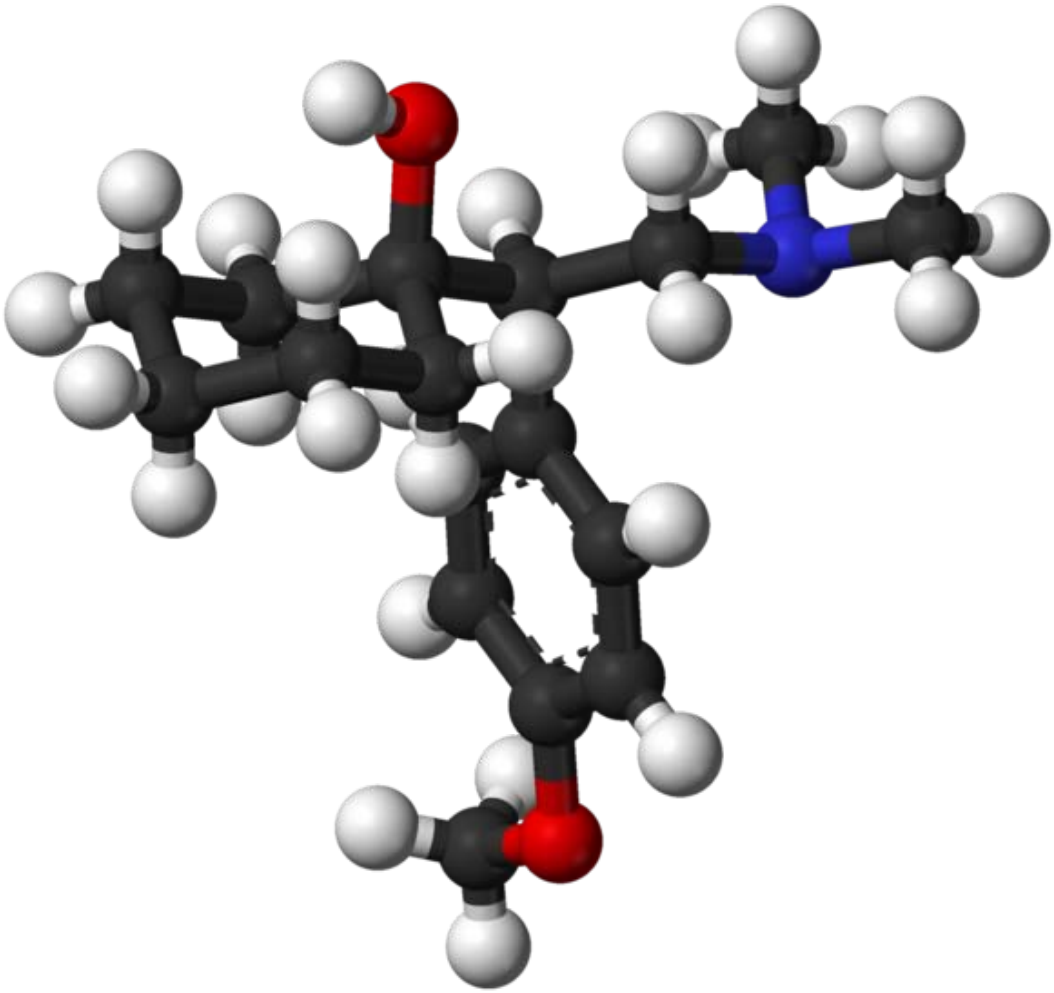
Strategies currently applied for improvement in pain management include framing it as an ethical issue; promoting pain management as a legal right, providing constitutional guarantees and statutory regulations that span negligence law, criminal law, and elder abuse; defining pain management as a fundamental human right, categorizing failure to provide pain management as professional misconduct, and issuing guidelines and standards of practice by professional bodies.

Chapter 13

Antidepressant



Fluoxetine (Prozac), an SSRI



Venlafaxine, an SNRI

An **antidepressant** is a psychiatric medication used to alleviate mood disorders, such as major depression and dysthymia and anxiety disorders such as social anxiety disorder. According to Gelder, Mayou &*Geddes (2005) people with a depressive illness will experience a therapeutic effect to their mood, however this will not be experienced in healthy individuals. Drugs including the monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) are most commonly associated with the term. These medications are among those most commonly prescribed by psychiatrists and other physicians, and their effectiveness and adverse effects are the subject of many studies and competing claims. Many drugs produce an antidepressant effect, but restrictions on their use have caused controversy and off-label prescription a risk, despite claims of superior efficacy.

The efficacy of modern thymoleptic anti-depressants has never been conclusively demonstrated to be greater than that of active placebo, according to two Cochrane Collaboration reviews. A review of all studies of anti-depressants ever submitted to the U.S. Food and Drug Administration (FDA), published and unpublished, was submitted to the FDA in 2004. In the published literature, anti-depressants had 94% success in treating depression. In the withheld literature, they had below 50% success. Combined, all studies showed 51% efficacy - only two points better than that of placebo. This increased the apparent efficacy of different anti-depressants from 11% to 69% over placebo. Possible exceptions are mirtazapine - a norepinephrine and serotonin antagonist - and venlafaxine, an SNRI with substantial similarity in chemical structure to the opioid derivative tramadol.

Opioids were used to treat major depression until the late 1950s. Amphetamines were used until the mid 1960s. Prescribing opioids or amphetamines for depression falls into a legal grey area. Research has only rarely been conducted in to the therapeutic potential of opioid derivatives for depression in the past sixty years, whereas amphetamines have found a thriving market for conditions as widely arrayed as attention deficit disorder, narcolepsy, and obesity, and continue to be studied for myriad applications. Both opioids and amphetamines induce a therapeutic response very quickly, showing results within twenty-four to forty-eight hours; the therapeutic ratios for both opioids and amphetamines are greater than those of the tricyclic anti-depressants. In some of this little, heavily restricted research, the opioid buprenorphine has shown the greatest potential for treating severe, treatment-resistant depression of any known pharmaceutical in a small study that is generally recognized and was published in 1995, but has never been pursued due to the social stigma attached to opioids in addition to that attached to mental illness in America.

Most typical antidepressants have a delayed onset of action (2–6 weeks) and are usually administered for anywhere from months to years. Despite the name, antidepressants are often used controversially, and with a dearth of empirical evidence to support their indication, off-label to treat other conditions, such as anxiety disorders, obsessive compulsive disorder, eating disorders, chronic pain, and some hormone-mediated disorders such as dysmenorrhea. Alone or together with anticonvulsants (e.g., Tegretol or Depakote), these medications can be used to treat attention-deficit hyperactivity disorder (ADHD) and substance abuse by addressing underlying depression. Also, antidepressants have been used sometimes to treat snoring and migraines.

Other medications that are not usually called antidepressants, including antipsychotics in low doses and benzodiazepines, may be used to manage depression, although benzodiazepines - along with all drugs called "anti-depressants" - cause a physical dependence to form. Stopping benzodiazepine (or SSRI) treatment abruptly can cause unpleasant withdrawal symptoms. An extract of the herb St John's Wort is commonly used as an antidepressant, although it is labeled as a dietary supplement in some countries. The term *antidepressant* is sometimes applied to any therapy (e.g., psychotherapy, electro-convulsive therapy, acupuncture) or process (e.g., sleep

disruption, increased light levels, regular exercise) found to improve a clinically depressed mood.

Inert placebos can have significant antidepressant effects, and so to establish a substance as an "antidepressant" in a clinical trial it is necessary to show superior efficacy to placebo.

History

St John's Wort

Various opiates (via the μ-opioid receptor and κ-opioid receptor) and amphetamines were commonly used as antidepressants until the mid-1950s, when they fell out of favor due to their addictive nature and side effects. Extracts from the herb St John's Wort have long been used (as a "nerve tonic") to alleviate depression.

Isoniazid and iproniazid

In 1951, two people from Sea View Hospital on Staten Island, Irving Selikoff and Edward Robitzek, began clinical trials on two new anti-tuberculosis agents from Hoffman-LaRoche, isoniazid and iproniazid. Only patients with a poor prognosis were initially treated; nevertheless, their condition improved dramatically. Selikoff and Robitzek noted "a subtle general stimulation . . . the patients exhibited renewed vigor and indeed this occasionally served to introduce disciplinary problems." The promise of a cure for tuberculosis in the Sea View Hospital trials was excitedly discussed in the

mainstream press. In 1952, learning of the stimulating side effects of isoniazid, the Cincinnati psychiatrist Max Lurie tried it on his patients. In the following year, he and Harry Salzer reported that isoniazid improved depression in two thirds of their patients and coined the term *antidepressant* to describe its action. A similar incident took place in Paris, where Jean Delay, head of psychiatry at Sainte-Anne Hospital, found out from his pulmonology colleagues at Cochin Hospital about the side effects of isoniazid. In 1952, before Lurie and Salzer, Delay, with the resident Jean-Francois Buisson, reported the positive effect of isoniazid on depressed patients. For reasons unrelated to its efficacy, isoniazid as an antidepressant was soon overshadowed by the more toxic iproniazid, although it remains a mainstay of tuberculosis treatment. The mode of antidepressant action of isoniazid is still unclear. It is speculated that its effect is due to the inhibition of diamine oxidase, coupled with a weak inhibition of monoamine oxidase A.

Another anti-tuberculosis drug tried at the same time by Selikoff and Robitzek, iproniazid, showed a greater "psychostimulant" effect, but more pronounced toxicity. After the publications on isoniazid, papers by Jackson Smith, Gordon Kamman, George Crane, and Frank Ayd appeared, describing the psychiatric applications of iproniazid. Ernst Zeller found iproniazid to be a potent monoamine oxidase inhibitor. Nevertheless, iproniazid remained relatively obscure until Nathan Kline, the influential and flamboyant head of research at Rockland State Hospital, began to popularize it in the medical and popular press as a "psychic energizer". Roche put a significant marketing effort behind iproniazid, including promoting its off-label use for depression. Its sales grew massively in the following years, until it was recalled from the market in 1961 due to cases of lethal hepatotoxicity.

Imipramine

The discovery that a tricyclic ("three ringed") compound had a significant antidepressant effect was first made in 1957 by Roland Kuhn in a Swiss psychiatric hospital. By that time antihistamine derivatives were increasingly used to treat surgical shock and then as psychiatric neuroleptics. Although in 1955 reserpine was shown to be more effective than placebo in alleviating anxious depression, neuroleptics (literally, "to seize the nerves" or "to take hold of nerves") were being developed as sedatives and antipsychotics.

Attempting to improve the effectiveness of chlorpromazine, Kuhn, in conjunction with the Geigy pharmaceutical company, discovered that compound "G 22355" (manufactured and patented in the US in 1951 by Häfliger and Schinder) had a beneficial effect in patients with depression accompanied by mental and motor retardation. Kuhn first reported his findings on what he called a "thymoleptic" (literally, "taking hold of the emotions," in contrast with neuroleptics, "taking hold of the nerves") in 1955-56. These gradually became established, resulting in marketing of the first tricyclic antidepressant, imipramine, soon followed by variants.

Later history

These new drug therapies became prescription drugs in the 1950s. It was estimated that no more than 50 to 100 people per million suffered from the kind of depression that these new drugs would treat, and pharmaceutical companies were not enthusiastic. Sales through the 1960s remained poor compared to the major tranquilizers (neuroleptics/antipsychotics) and minor tranquilizers (such as benzodiazepines), which were being marketed for different uses. Imipramine remained in common use and numerous successors were introduced. The field of MAO inhibitors remained quiet for many years until "reversible" forms affecting only the MAO-A subtype were introduced, avoiding some of the adverse effects.

Most pharmacologists by the 1960s thought the main therapeutic action of tricyclics was to inhibit norepinephrine reuptake, but it was gradually observed that this action was associated with energizing and motor stimulating effects, while some antidepressant compounds appeared to have differing effects through action on serotonin systems (notably proposed in 1969 by Carlsson and Lindqvist as well as Lapin and Oxenkrug).

Researchers began a process of rational drug design to isolate antihistamine-derived compounds that would selectively target these systems. The first such compound to be patented was zimelidine in 1971, while the first released clinically was indalpine. Fluoxetine was approved for commercial use by the Food and Drug Administration (United States) in 1988, becoming the first blockbuster SSRI. Fluoxetine was developed at Eli Lilly and Company in the early 1970s by Bryan Molloy, David Wong and others.

While it had fallen out of favor in most countries through the 19th and 20th centuries, the herb St John's Wort became increasingly popular in Germany, where Hypericum extracts were eventually licensed, packaged and prescribed by doctors. Small-scale efficacy trials were carried out in the 1970s and 1980s, and attention grew in the 1990s following a meta-analysis of these. It remained an over-the-counter drug (OTC) or supplement in most countries and research continued to investigate its neurotransmitter effects and active components, particularly hyperforin

SSRIs became known as "novel antidepressants" along with other newer drugs such as SNRIs and NRIs with various different selective effects, such as venlafaxine, duloxetine, nefazodone and mirtazapine.

Types of antidepressants

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants considered the current standard of drug treatment. A possible cause of depression is an inadequate amount of serotonin, a chemical used in the brain to transmit signals between neurons. SSRIs are said to work by preventing the reuptake of serotonin (also known as 5-hydroxytryptamine, or 5-HT) by the presynaptic neuron, thus maintaining higher levels

of 5-HT in the synapse. Chemists Klaus Schmiegel and Bryan Molloy of Eli Lilly discovered the first SSRI, fluoxetine. This class of drugs includes:

- Citalopram (Celexa, Cipramil)
- Escitalopram (Lexapro, Cipralex, Seroplex, Lexamil)
- Fluoxetine (Prozac, Sarafem, Symbyax)
- Fluvoxamine (Luvox)
- Paroxetine (Paxil, Aropax)
- Sertraline (Zoloft)

These antidepressants typically have fewer adverse effects than the tricyclics or the MAOIs, although such effects as drowsiness, dry mouth, nervousness, anxiety, insomnia, decreased appetite, long-term weight gain and decreased ability to function sexually may occur. Some side effects may decrease as a person adjusts to the drug, but other side effects may be persistent. Though safer than first generation antidepressants, SSRIs may not work on as many patients as previous classes of antidepressants, suggesting the role of norepinephrine in depression is still important.

Work by two researchers has called into question the link between serotonin deficiency and symptoms of depression, noting that the efficacy of SSRIs as treatment does not in itself prove the link. Research indicates that these drugs may interact with transcription factors known as "clock genes", which may play a role in the addictive properties of drugs (drug abuse), and possibly in obesity.

A systematic review of randomized controlled trials published in the Archives of General Psychiatry showed that up to one-third of the 6-week effect of SSRI Treatment can be seen in the first week. The same study also found that patients treatment with SSRIs were 64% more likely to achieve a 50% absolute reduction in HRSD than patients given a placebo.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a newer form of antidepressant that work on both norepinephrine and 5-HT. They typically have similar side effects to the SSRIs, though there may be a withdrawal syndrome on discontinuation that may necessitate dosage tapering. These include:

- Desvenlafaxine (Pristiq)
- Duloxetine (Cymbalta)
- Milnacipran (Ixel)
- Venlafaxine (Effexor)

Noradrenergic and specific serotonergic antidepressants (NaSSAs)

Noradrenergic and specific serotonergic antidepressants (NaSSAs) form a newer class of antidepressants which purportedly work to increase norepinephrine (noradrenaline) and

serotonin neurotransmission by blocking presynaptic alpha-2 adrenergic receptors while at the same time blocking certain serotonin receptors. Side effects may include drowsiness, increased appetite, and weight gain. Examples include:

- Mianserin (Tolvon)
- Mirtazapine (Remeron, Avanza, Zispin)

Norepinephrine (noradrenaline) reuptake inhibitors (NRIs)

Norepinephrine (noradrenaline) reuptake inhibitors (NRIs) act via norepinephrine (also known as *noradrenaline*). NRIs are thought to have a positive effect on the concentration and motivation in particular. These include:

- Atomoxetine (Strattera)
- Mazindol (Mazanor, Sanorex)
- Reboxetine (Edronax)
- Viloxazine (Vivalan)

Norepinephrine-dopamine reuptake inhibitors (NDRIs)

Norepinephrine-dopamine reuptake inhibitors inhibit the neuronal reuptake of dopamine and norepinephrine (noradrenaline). These include:

- Bupropion (Wellbutrin, Zyban)

Selective serotonin reuptake enhancers (SSREs)

- Tianeptine (Stablon, Coaxil, Tatinol)

Norepinephrine-dopamine disinhibitors (NDDIs)

Norepinephrine-dopamine disinhibitors (NDDIs) act by antagonizing the serotonin 5-HT_{2C} receptor which normally acts to inhibit norepinephrine and dopamine release, thereby promoting outflow of these neurotransmitters.

- Agomelatine (Valdoxan, Melitor, Thymanax)

Tricyclic antidepressants (TCAs)

Tricyclic antidepressants are the oldest class of antidepressant drugs. Tricyclics block the reuptake of certain neurotransmitters such as norepinephrine (noradrenaline) and serotonin. They are used less commonly now due to the development of more selective and safer drugs. Side effects include increased heart rate, drowsiness, dry mouth, constipation, urinary retention, blurred vision, dizziness, confusion, and sexual dysfunction. Toxicity occurs at approximately ten times normal dosages; these drugs are often lethal in overdoses, as they may cause a fatal arrhythmia. However, tricyclic

antidepressants are still used because of their effectiveness, especially in severe cases of major depression. These include:

Tertiary amine tricyclic antidepressants:

- Amitriptyline (Elavil, Endep)
- Clomipramine (Anafranil)
- Doxepin (Adapin, Sinequan)
- Imipramine (Tofranil)
- Trimipramine (Surmontil)

Secondary amine tricyclic antidepressants

- Desipramine (Norpramin)
- Nortriptyline (Pamelor, Aventyl, Noritren)
- Protriptyline (Vivactil)

Monoamine oxidase inhibitor (MAOIs)

Monoamine oxidase inhibitors (MAOIs) may be used if other antidepressant medications are ineffective. MAOIs work by blocking the enzyme monoamine oxidase which breaks down the neurotransmitters dopamine, serotonin, and norepinephrine (noradrenaline). Because there are potentially fatal interactions between this class of medication and certain foods (particularly those containing tyramine), as well as certain drugs, classic MAOIs are rarely prescribed anymore. However, this does not apply to Emsam, the transdermal patch form of selegiline, which due to its bypassing of the stomach has a lesser propensity to induce such events. MAOIs can be as effective as tricyclic antidepressants, although they are generally used less frequently due to the fact that they have a higher incidence of dangerous side effects and interactions. A new generation of MAOIs has been introduced; moclobemide (Manerix), known as a reversible inhibitor of monoamine oxidase A (RIMA), acts in a more short-lived and selective manner and does not require a special diet. The MAOI group of medicines include:

- Isocarboxazid (Marplan)
- Moclobemide (Aurorix, Manerix)
- Phenelzine (Nardil)
- Selegiline (Eldepryl, Emsam)
- Tranylcypromine (Parnate)

Augmenter drugs

Some antidepressants have been found to work better in some patients when used in combination with another drug. Such "augmenter" drugs include:

- Buspirone (Buspar)
- Gepirone (Ariza)

- Nefazodone (Serzone)
- Tandospirone (Sediel)
- Trazodone (Desyrel)
- Bupropion (Wellbutrin/Zyban)

Tranquillizers and sedatives, typically the benzodiazepines, are prescribed to ease anxiety and promote sleep. Because of the high risk of dependency, these medications are intended only for short-term or occasional use. Medications are often used not for their primary functions, but to exploit what are normally side effects. Quetiapine fumarate (Seroquel) is designed primarily to treat schizophrenia and bipolar disorder, but frequently causes somnolence because of its affinity for histamine (H1 and H2) receptors, exploiting the same side effects as diphenhydramine (Benadryl).

Antipsychotics such as risperidone (Risperdal), olanzapine (Zyprexa), and quetiapine (Seroquel) are prescribed as mood stabilizers and to treat anxiety. Their use as mood stabilizers is a recent phenomenon, and controversial among some patients. Antipsychotics, whether typical or atypical, may also be prescribed to augment an antidepressant, to increase the blood concentration of another drug, or to relieve the psychotic or paranoid symptoms that often accompany clinical depression. However, they can cause serious side effects, particularly at high dosages, including blurred vision, muscle spasms, restlessness, tardive dyskinesia, and weight gain.

Psychostimulants are sometimes added to an antidepressant regimen if the patient suffers from anhedonia, hypersomnia and/or excessive eating as well as low motivation. These symptoms are common in atypical depression, and can be resolved by adding low to moderate doses of amphetamine (Adderall), methylphenidate (Ritalin) or modafinil (Provigil, Alertec), as these chemicals can enhance motivation and social behavior, and suppress appetite and sleep. Modafinil is unique in its effect on sleep: it increases alertness and reduces drowsiness while the patient is active, but does not inhibit normal sleep. These medications can also restore sexual drive, although this is a negative side effect and not a reason for the prescription of psychostimulants. Extreme caution must be used however with certain populations. Stimulants are known to trigger manic episodes in people suffering from bipolar disorder. Close supervision of those with substance abuse disorders is urged. Emotionally labile patients should avoid stimulants, as they exacerbate mood shifting.

Lithium remains the standard treatment for bipolar disorder and is often used in conjunction with other medications, depending on whether mania or depression is being treated. Lithium's potential side effects include thirst, tremors, light-headedness, nausea, and diarrhea. Some of the anticonvulsants, such as carbamazepine (Tegretol), sodium valproate (Epilim), and lamotrigine (Lamictal), are also used as mood stabilizers, particularly in bipolar disorder. Both lithium and lamotrigine have also been studied and used to augment antidepressants in treatment-resistant unipolar depression.

Herbal antidepressants

St. John's Wort is by far the most widely-used and well-studied herbal antidepressant. A number of other herbs have been used traditionally to treat depression and related ailments like anxiety, but the research on most of these treatments is sparse.

Saffron (*Crocus sativus L.*) has been found in a double-blind randomized clinical trial to be equally effective with imipramine for treating mild to moderate depression; the study also remarked that anticholinergic side effects were more frequent in the imipramine treatment group. Another 8-week double-blind randomized trial found saffron to have a similar effect to fluoxetine (Prozac) in the treatment of mild to moderate depression, including a similar remission rate and similar rate of side effects.

Lavender, *Lavandula angustifolia*, has been traditionally used to treat depression, although until recently there was little research on this plant. A 2003 double-blind, randomized clinical trial compared lavender to imipramine in the treatment of mild to moderate depression, testing both each treatments individually, and a combination of the two. Lavender was found to be less effective than imipramine, but the combination of both treatments was found to be more effective than either alone.

Several plants in the *Salvia* genus have been studied for antidepressant properties, although most of the research conducted so far has only been from mice and rat studies. Salvia elegans, also known as pineapple sage, is widely used in Mexican traditional medicine, and has been found in single study in mice to have antidepressant and antianxiety properties. Salvia sclarea, also known as clary, is known to have an antidepressant-like effect in rats, which is thought to be explained by modulation of dopamine.

Ocimum tenuiflorum, also known as Tulsi or holy basil, has been used in Ayurveda to treat anxiety and depression, and was shown in a clinical study to be effective at treating generalized anxiety disorder and depression.

Wormwood, *Artemisia absinthium*, has shown antidepressant effects in mice, similar activity to imipramine.

Nutrients and nutritional supplements as antidepressants

Nutrition has been implicated as one of the causes and risk factors for depression, and accordingly, one approach to depression involves the use of nutritional supplements or changes in diet. A study of older adults found that poor nutrition was a strong predictor of depressive symptoms a year later. A few nutrients have been studied directly for their antidepressant properties, both to treat and prevent depression, as well as related conditions such as anxiety.

Omega-3

Omega 3 fatty acids have been proposed as a treatment for depression, often suggested to be combined with other treatments. One small pilot study of childhood depression (ages 6–12) suggested that omega 3 may have therapeutic benefits for treating childhood depression. A 2005 review of the scientific literature concluded that there were several different independent lines of evidence suggesting that omega-3 fatty acids play a role in depression, and that the theory of omega-3's role in depression was biologically plausible. The evidence includes a few double-blind randomized control trials, epidemiological studies linking low fish consumption (the primary source of omega-3) to increased rates of depression, and case-control and cohort studies of unipolar and postpartum depression indicating low blood levels of omega-3 in depressed patients.

Other essential nutrients

Folic acid and Vitamin B12 have also been proposed as a treatment for depression, especially when used in conjunction with other treatments. In particular, folic acid has been shown to improve the treatment response to other antidepressants.

Prescription trends

In the United Kingdom the use of antidepressants increased by 234% in the 10 years up to 2002. In the United States a 2005 independent report stated that 11% of women and 5% of men in the non-institutionalized population (2002) take antidepressants A 1998 survey found that 67% of patients diagnosed with depression were prescribed an antidepressant. A 2007 study suggested that 25% of Americans were overdiagnosed with depression, regardless of any medical intervention. The findings were based on a national survey of 8,098 people.

A 2002 survey found that about 3.5% of all people in France were being prescribed antidepressants, compared to 1.7% in 1992, often for conditions other than depression and often not in line with authorizations or guidelines Between 1996 and 2004 in British Columbia, antidepressant use increased from 3.4% to 7.2% of the population. Data from 1992 to 2001 from the Netherlands indicated an increasing rate of prescriptions of SSRIs, and an increasing duration of treatment. Surveys indicate that antidepressant use, particularly of SSRIs, has increased rapidly in most developed countries, driven by an increased awareness of depression together with the availability and commercial promotion of new antidepressants. Antidepressants are also increasingly used worldwide for non-depressive patients as studies continue to show the potential of immunomodulatory, analgesic and anti-inflammatory properties in antidepressants.

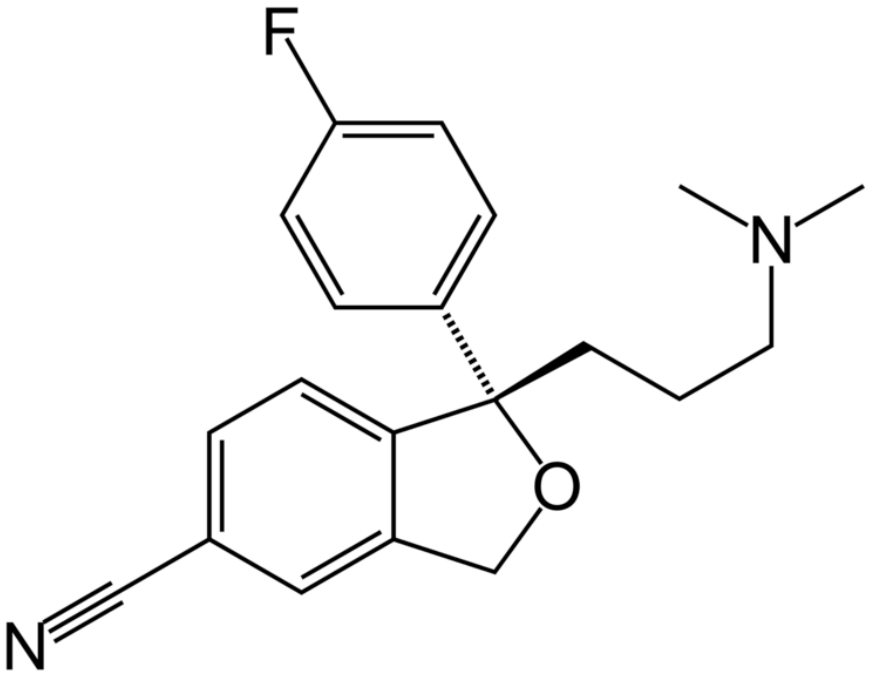
The choice of particular antidepressant is reported to be based, in the absence of research evidence of differences in efficacy, on seeking to avoid certain side effects, and taking into account comorbid (co-occurring) psychiatric disorders, specific clinical symptoms and prior treatment history.

It is also reported that, despite equivocal evidence of a significant difference in efficacy between older and newer antidepressants, clinicians perceive the newer drugs, including SSRIs and SNRIs, to be more effective than the older drugs (tricyclics and MAOIs). A survey in the UK found that male general physicians were more likely to prescribe antidepressants than female doctors.

The number of antidepressants prescribed by the NHS in the United Kingdom almost doubled during one decade, authorities reported in 2010. Furthermore the number highly increased in 2009 when 39.1 million prescriptions were issued compared with 20.1 million issued in 1999. Also, physicians issued 3.18 million more prescriptions in 2009 than in 2008. Health authorities believed the increase was partly linked to the recession. However, other reasons include a diagnosis improvement, a reduction of the stigma on mental ill-health, and more distress caused by the economic crisis. Furthermore, physicians concern is that some people who exhibit milder symptoms of depression are being prescribed drugs unnecessarily due to the lack of other options including talking therapies, counseling and cognitive behavior therapy. One more factor that may be increasing the consumption of antidepressants is the fact that these medications now are used for other conditions including social anxiety and post traumatic stress.

The use of antidepressants in the United States doubled over one decade, from 1996 to 2005. Antidepressant drugs were prescribed to 13 million in 1996 and to 27 million people by 2005. In 2008, more than 164 million prescriptions were written. During this period, patients were less likely to undergo psychotherapy.

Most commonly prescribed antidepressants



Structural formula of the SSRI escitalopram, in its free base form

The most commonly prescribed antidepressants in the US retail market in 2007 were:

Drug	Brand	Class	2007 Prescriptions (in millions)
Sertraline	Zoloft	SSRI	29.652
Escitalopram	Lexapro	SSRI	27.023
Fluoxetine	Prozac	SSRI	22.266
Bupropion	Wellbutrin	NDRI	20.184
Paroxetine	Paxil	SSRI	18.141
Venlafaxine	Effexor	SNRI	17.200
Citalopram	Celexa	SSRI	16.246
Trazodone	Desyrel	SARI	15.473
Amitriptyline	Elavil	TCA	13.462
Duloxetine	Cymbalta	SNRI	12.551
Mirtazapine	Remeron	TeCA	5.129
Nortriptyline	Pamelor	TCA	3.105
Imipramine	Tofranil	TCA	1.524

The most commonly prescribed antidepressant in Germany is reported to be (concentrated extracts of) hypericum perforatum (St John's Wort). In the Netherlands, paroxetine, marketed as Seroxat among generic preparations, is the most prescribed antidepressant, followed by the tricyclic antidepressant amitriptyline, citalopram and venlafaxine.

Mechanisms of action

The therapeutic effects of antidepressants are believed to be caused by their effects on neurotransmitters and neurotransmission.

The Monoamine Hypothesis is a biological theory stating that depression is caused by the underactivity in the brain of monoamines, such as dopamine, serotonin, and norepinephrine. In the 1950s the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants were accidentally discovered to be effective in the treatment of depression. These findings and other supporting evidence led Joseph Schildkraut to publish his paper called "The Catecholamine Hypothesis of Affective Disorders" in 1965. Schildkraut associated low levels of neurotransmitters with depression. Research into other mental impairments such as schizophrenia also found that too little activity of certain neurotransmitters were connected to these disorders. The hypothesis has been a major focus of research in the fields pathophysiology and pharmacotherapy for over 25 years.

Monoamine oxidase inhibitors (MAOIs) block the degradation of the monoamine neurotransmitters serotonin, norepinephrine, and dopamine by inhibiting the enzyme

monoamine oxidase, leading to increased concentrations of these neurotransmitters in the brain and an increase in neurotransmission.

Tricyclic antidepressants (TCAs) prevent the reuptake of various neurotransmitters, including serotonin, norepinephrine, and to a much less extent, dopamine. Nowadays the most common antidepressants are selective serotonin reuptake inhibitors (SSRIs), which prevent the reuptake of serotonin (thereby increasing the level of active serotonin in synapses of the brain). Other novel antidepressants affect norepinephrine reuptake, or different receptors on the nerve cell.

While MAOIs, TCAs and SSRIs increase serotonin levels, others prevent serotonin from binding to 5-HT_{2A} receptors, suggesting it is too simplistic to say serotonin is a happy hormone. In fact, when the former antidepressants build up in the bloodstream and the serotonin level is increased, it is common for the patient to feel worse for the first weeks of treatment. One explanation of this is that 5-HT_{2A} receptors evolved as a saturation signal (people who use 5-HT_{2A} antagonists often gain weight), telling the animal to stop searching for food, a mate, etc., and to start looking for predators. In a threatening situation it is beneficial for the animal not to feel hungry even if it needs to eat. Stimulation of 5-HT_{2A} receptors will achieve that. But if the threat is long lasting the animal needs to start eating and mating again - the fact that it survived shows that the threat was not so dangerous as the animal felt. So the number of 5-HT_{2A} receptors decreases through a process known as downregulation and the animal goes back to its normal behavior. This suggests that there are two ways to relieve anxiety in humans with serotonergic drugs: by blocking stimulation of 5-HT_{2A} receptors or by overstimulating them until they decrease via tolerance.

The stimulation or blocking of different receptors on a cell affects its genetic expression. Recent findings have shown that neurogenesis, and thus, changes in brain morphogenesis, mediate the effects of antidepressant drugs.

Another hypothesis is that antidepressants may have some longer-term effects due to the promotion of neurogenesis in the hippocampus, an effect found in mice. Other animal research suggests that antidepressants can affect the expression of genes in brain cells, by influencing "clock genes".

Other research suggests that delayed onset of clinical effects from antidepressants indicates involvement of adaptive changes in antidepressant effects. Rodent studies have consistently shown upregulation of the 3, 5-cyclic adenosine monophosphate (cAMP) system induced by different types of chronic but not acute antidepressant treatment, including serotonin and norepinephrine uptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, lithium and electroconvulsions. cAMP is synthesized from adenosine 5-triphosphate (ATP) by adenylyl cyclase and metabolized by cyclic nucleotide phosphodiesterases (PDEs). Data also suggest that antidepressants can modulate neural plasticity in longterm administration.

One theory regarding the cause of depression is that it is characterized by an overactive hypothalamic-pituitary-adrenal axis (HPA axis) that resembles the neuro-endocrine (cortisol) response to stress. These HPA axis abnormalities participate in the development of depressive symptoms, and antidepressants serve to regulate HPA axis function.

Comparison

A number of antidepressants have been compared below:

Compound	SERT	NET	DAT	H_1	M_{1-5}	α_1	α_2	5-HT_{1A}	5-HT_2	D_2
Agomelatine	?	?	?	?	?	?	?	?	270	?
Amitriptyline	4.3	35	3250	0.95	9.6	24	690	450	18	1460
Amoxapine	58	16	4310	25	1000	50	2600	?	?	?
Atomoxetine	8.9	2.03	1080	5500	2060	3800	8800	10900	940	35000+
Bupropion	45026	1389	2784	11800	35000+	4200	35000+	35000+	35000+	35000+
Buspirone	?	?	?	?	?	138	?	5.7	174	362
Butriptyline	1360	5100	3940	?	?	?	?	?	?	?
Citalopram	1.16	4070	28100	?	?	?	?	?	?	?
Clomipramine	0.28	38	2190	31	37	38	3200	?	?	?
Desipramine	17.6	0.83	3190	60	66	100	5500	6400	350	3500
Dosulepin	8.6	46	5310	?	?	?	?	?	?	?
Doxepin	68	29.5	12100	0.17	23	23.5	1270	276	27	360
Duloxetine	0.8	7.5	240	?	?	?	?	?	?	?
Etoperidone	890	20000	52000	3100	35000+	38	570	85	36	2300
Femoxetine	11	760	2050	4200	184	650	1970	2285	130	590
Fluoxetine	0.81	240	3600	5400	590	3800	13900	32400	280	12000
Fluvoxamine	0.81	240	3600	?	?	?	?	?	?	?
Imipramine	1.4	37	8500	37	46	32	3100	5800	150	620
Lofepramine	70	5.4	18000	360	67	100	2700	4600	200	2000
Maprotiline	5800	11.1	1000	2	570	90	9400	?	?	?
Mazindol	100	1.4	11	?	?	?	?	?	?	?
Mianserin	4000	71	9400	?	?	?	?	?	?	?
Milnacipran	123	200	10000+	?	?	?	?	?	?	?
Mirtazapine	1500+	1250~	1500+	1~	1000~	500~	100~	1500+	10~	1500+
Nefazodone	200	360	360	24000	11000	48	640	80	26	910
Nisoxetine	383	5.1	477	?	?	?	?	?	?	?
Nomifensine	1010	15.6	56	?	?	?	?	?	?	?
Nortriptyline	18	4.37	1140	6.3	37	55	2030	294	41	2570
Oxaprotiline	3900	4.9	4340	?	?	?	?	?	?	?
Paroxetine	0.13	40	490	22000	108	4600	17000	35000+	19000	32000
Protriptyline	19.6	1.41	2100	25	25	130	6600	?	?	?

Reboxetine	720	11	10000+	?	?	?	?	?	?	?
Sertraline	0.29	420	25	24000	630	380	4100	35000+	9900	10700
Trazodone	160	8500	7400	1100	35000+	42	320	96	25.0	35000+
Trimipramine	149	2450	3780	0.27	58	24	680	?	?	?
Venlafaxine	82	2480	7647	35000+	35000+	35000+	35000+	35000+	35000+	35000+
Viloxazine	17300	155	100000+	?	?	?	?	?	?	?
Zimelidine	152	9400	11700	?	?	?	?	?	?	?

The values above are expressed as equilibrium dissociation constants. It should be noted that less is more. SERT, NET, and DAT correspond to the abilities of the compounds to inhibit the reuptake of serotonin, norepinephrine, and dopamine, respectively. The other values correspond to their affinity for various receptors.

Anti-inflammatory and immunomodulation

Recent studies show pro-inflammatory cytokine processes take place during clinical depression, mania and bipolar disorder, and it is possible that symptoms of these conditions are attenuated by the pharmacological effect of antidepressants on the immune system.

Studies also show that the chronic secretion of stress hormones as a result of disease, including somatic infections or autoimmune syndromes, may reduce the effect of neurotransmitters or other receptors in the brain by cell-mediated pro-inflammatory pathways, thereby leading to the dysregulation of neurohormones. SSRIs, SNRIs and tricyclic antidepressants acting on serotonin, norepinephrine and dopamine receptors have been shown to be immunomodulatory and anti-inflammatory against pro-inflammatory cytokine processes, specifically on the regulation of Interferon-gamma (IFN-gamma) and Interleukin-10 (IL-10), as well as TNF-alpha and Interleukin-6 (IL-6). Antidepressants have also been shown to suppress TH1 upregulation.

Antidepressants, specifically TCAs and SNRIs (or SSRI-NRI combinations), have also shown analgesic properties.

These studies warrant investigation for antidepressants for use in both psychiatric and non-psychiatric illness and that a psycho-neuroimmunological approach may be required for optimal pharmacotherapy. Future antidepressants may be made to specifically target the immune system by either blocking the actions of pro-inflammatory cytokines or increasing the production of anti-inflammatory cytokines.

Therapeutic efficacy

There is a large amount of research evaluating the potential therapeutic effects of antidepressants, whether through efficacy studies under experimental conditions (including randomized clinical trials) or through studies of "real world" effectiveness. A sufficient *response* to a drug is often defined as at least a 50% reduction in self-reported

or observed symptoms, with a *partial response* often defined as at least a 25% reduction. The term *remission* indicates a virtual elimination of depression symptoms, albeit with the risk of a *recurrence* of symptoms or complete *relapse*. Full remission or *recovery* signifies a full sustained return to a "normal" psychological state with full functioning.

There has also been a great deal of study about whether antidepressants address the underlying causes of depression. A 2002 review concluded that there was no evidence that antidepressants reduce the risk of recurrence of depression when their use is terminated. The authors of this review advocated that antidepressants be combined with therapy, and pointed to Interpersonal Psychotherapy (IPT) and Cognitive Behavioral Therapy (CBT).

Review studies

Recent clinical reviews include:

- A comparison of the relative efficacy of different classes of antidepressants in different settings and in regard to different kinds of depression
- An assessment of antidepressants compared with an "active placebo"
- An assessment of the newer types of the MAOI class
- A meta-analysis of randomized trials of St John's Wort
- A review of the use of antidepressants for childhood depression
- A review of all antidepressant trials submitted to the U.S. FDA from 1987 to 2004 has shown that around half of the trials failed to show any benefit over placebo. All but one of the successful trial results were published in scientific journals, while nearly all the unsuccessful trials were either not published or were presented in a misleadingly positive light (compared to the FDA's own evaluation of the data). This arose because whilst studies are required for medical approval, studies showing adverse findings are not necessarily required to be published or (if published) given similar prominence. As a result, while it appeared in the research literature that 94 percent of trials had positive outcomes, in the actual data submitted to the Food and Drug Administration, only 51 percent did. This publication bias inflated the apparent statistical effect of every antidepressant studied, by between 11% and 69%.
- A meta-analysis by UK, US and Canadian researchers, published in 2008, surveyed all pharmaceutical-company-sponsored drug trials on the six most widely prescribed new-generation antidepressants submitted for approval to the FDA between 1987 and 1999. The results showed, consistent with a prior metaanalysis, that the difference in efficacy between antidepressants and placebo was minimal, but that it increased from virtually no difference at moderate levels of initial depression to a relatively small difference for patients with very severe depression. The difference reached conventional criteria for clinical significance for patients at the upper end of the very severely depressed category, due to a reduction in the efficacy of placebo. The study received widespread media coverage in some countries, but was met with criticism from the professional community. Eli Lilly and Company responded by highlighting that the study did

not take into account more recent studies on its product, Prozac, and that it was proud of the difference Prozac has made to millions of people. GlaxoSmithKline warned that this one study should not be used to cause unnecessary alarm and concern for patients. Wyeth pointed out that the data were good enough for FDA approval of the drugs. Two leading UK psychiatrists/pharmacologists, with financial and professional links to pharmaceutical companies, argued that short-term approval trials are not very suitable for evaluating effectiveness, that the unpublished ones are poorer quality, that the meta-analysis authors came from a "psychology background" rather than drug testing background, and that the media and "elements of the medico/scientific community" have "a down on antidepressants" and that the media does not appreciate the seriousness of depression and blames and stigmatizes sufferers in a manner rooted in medieval religious attitudes.

- A May 7, 2002 article in The Washington Post titled "Against Depression, a Sugar Pill Is Hard to Beat" stated, "A new analysis has found that in the majority of trials conducted by drug companies in recent decades, sugar pills have done as well as—or better than—antidepressants. Companies have had to conduct numerous trials to get two that show a positive result, which is the Food and Drug Administration's minimum for approval. What's more, the sugar pills, or placebos, cause profound changes in the same areas of the brain affected by the medicines, according to research published last week... the makers of Prozac had to run five trials to obtain two that were positive, and the makers of Paxil and Zoloft had to run even more... When Leuchter compared the brain changes in patients on placebos, he was amazed to find that many of them had changes in the same parts of the brain that are thought to control important facets of mood... Once the trial was over and the patients who had been given placebos were told as much, they quickly deteriorated. People's belief in the power of antidepressants may explain why they do well on placebos..."

Clinical guidelines

The American Psychiatric Association 2000 Practice Guideline for the Treatment of Patients with Major Depressive Disorder indicates that, if preferred by the patient, antidepressant medications may be provided as an initial primary treatment for mild major depressive disorder; antidepressant medications should be provided for moderate to severe major depressive disorder unless electroconvulsive therapy is planned; and a combination of antipsychotic and antidepressant medications or electroconvulsive therapy should be used for psychotic depression. It states that efficacy is generally comparable between classes and within classes and that the initial selection will largely be based on the anticipated side effects for an individual patient, patient preference, quantity and quality of clinical trial data regarding the medication, and its cost.

The UK National Institute for Clinical Excellence (NICE) 2004 guidelines indicate that antidepressants should not be used for the initial treatment of mild depression, because the risk-benefit ratio is poor; that for moderate or severe depression an SSRI is more likely to be tolerated than a tricyclic; and that antidepressants for severe depression

should be combined with a psychological treatment such as Cognitive Behavioural Therapy.

Efficacy limitations and strategies

Between 30% and 50% of individuals treated with a given antidepressant do not show a response. Even where there has been a robust response, significant continuing depression and dysfunction is common, with relapse rates 3 to 6 times higher in such cases. In addition, antidepressant drugs tend to lose efficacy over the course of treatment. A number of strategies are used in clinical practice to try to overcome these limits and variations.

"Trial and error" switching

The American Psychiatric Association 2000 Practice Guideline advises that where no response is achieved following six to eight weeks of treatment with an antidepressant, to switch to an antidepressant in the same class, then to a different class of antidepressant.

A recent meta-analysis review found wide variation in the findings of prior studies; for patients who had failed to respond to an SSRI antidepressant, between 12% and 86% showed a response to a new drug, with between 5% and 39% ending treatment due to adverse effects. The more antidepressants an individual had already tried, the less likely they were to benefit from a new antidepressant trial.

Augmentation and combination

For a partial response, the American Psychiatric Association guidelines advise adding a different kind of pharmaceutical agent to the antidepressant. Studies suggest that most patients fail to achieve remission on a given antidepressant, and augmentation strategies used in clinical practice include the use of lithium and thyroid augmentation, but there is not a good evidence base for these practices or for more novel strategies such as the use of selective dopamine agonists, sex steroids, NRI's, glucocorticoid-specific agents, or the newer anticonvulsants

A combination strategy involves adding one or more additional antidepressants, usually from different classes so as to have a diverse neurochemical effect. Although this may be used in clinical practice, there is little evidence for the relative efficacy or adverse effects of this strategy.

Long-term use

The therapeutic effects of antidepressants typically do not continue once the course of medication ends, resulting in a high rate of relapse. A recent meta-analysis of 31 placebo-controlled antidepressant trials, mostly limited to studies covering a period of one year, found that 18% of patients who had responded to an antidepressant relapsed while still taking it, compared to 41% whose antidepressant was switched for a placebo. The

American Psychiatric Association guidelines advise four to five months of continuation treatment on an antidepressant following the resolution of symptoms. For patients with a history of depressive episodes, the British Association for Psychopharmacology's 2000 Guidelines for Treating Depressive Disorders with Antidepressants advise remaining on an antidepressant for at least six months and as long as five years or indefinitely.

Whether or not someone relapses after stopping an antidepressant does not appear to be related to the duration of prior treatment, however, and gradual loss of therapeutic benefit during the course also occurs. A strategy involving the use of pharmacotherapy in the treatment of the acute episode, followed by psychotherapy in its residual phase, has been suggested by some studies.

Medication failure

Approximately 30% of patients have remission of depression with medications. For patients with inadequate response, either adding sustained-release bupropion (initially 200 mg per day then increase by 100 mg up to total of 400 mg per day) or buspirone (up to 60 mg per day) for augmentation as a second drug can cause remission in approximately 30% of patients, while switching medications can achieve remission in about 25% of patients.

By pregnancy

There is uncertainty whether pregnancy contributes to medication failure, because the only report so far has drawn much controversy on itself:

In 2006, a widely reported study published in the *Journal of the American Medical Association* (*JAMA*) challenged the common assumption that hormonal changes during pregnancy protected expectant mothers against depression, finding that discontinuing anti-depressive medication during pregnancy led to more frequent relapse. The *JAMA* article did not disclose that several authors had financial ties to pharmaceutical companies making antidepressants. The *JAMA* later published a correction noting the ties and the authors maintain that the ties have no bearing on their research work. Obstetrician and perinatologist Adam Urato told the *Wall Street Journal* that patients and medical professionals need advice free of industry influence.

Withdrawal symptoms

In general, it may be impossible or very difficult to stop many antidepressant medications safely because nearly irreversible changes caused to central nervous system. These withdrawal symptoms can be reason for worsening of depression, manic or aggressive symptoms or suicide. When prescribing antidepressants, doctors don't often properly describe these withdrawal problems to patients with serious mental health problems.

If an SSRI medication is suddenly discontinued, it may produce both somatic and psychological withdrawal symptoms, a phenomenon known as "SSRI discontinuation

syndrome" (Tamam & Ozpoyraz, 2002). When the decision is made to stop taking antidepressants it is common practice to "wean" off of them by slowly decreasing the dose over a period of several weeks. Most cases of discontinuation syndrome last between one and four weeks.

The selection of an antidepressant and dosage suitable for a certain case and a certain person is a lengthy and complicated process, requiring the knowledge of a professional. Certain antidepressants can initially make depression worse, can induce anxiety, or can make a patient aggressive, dysphoric or acutely suicidal. In rare cases, an antidepressant can induce a switch from depression to mania or hypomania.

Anecdotal evidence seems to show that many antidepressants can be withdrawn without major withdrawal symptoms if discontinued within the first week of treatment.

Chapter 14

Rebox Electrotherapy and Patient-Controlled Analgesia

Rebox electrotherapy

Rebox electrotherapeutic method is based on non-invasive transcutaneous application of specific electric currents to a living tissue. Main indications for using the Rebox include treatment of acute and chronic pain, immobility, musculoskeletal and neurological disorders and oedema.

Method description

Rebox electrotherapeutic rehabilitation has been clinically used in human and animal medicine since 1985. It was invented and patented by *Ing. Petr Slovak, Ph.D.*, a lecturer at Czech Technical University in Prague, CZ. The name Rebox is derived from the "Rehabilitation Box".

Rebox method is different from classic Transcutaneous Electric Nerve Stimulations (TENS) in many basic characteristics. Specific impulses (frequency 2–4 kHz, pulse width 100-300 μs) of weak electric currents (100-200 μA) are introduced transcutaneously to the affected region with a touch of a small non-invasive **treatment electrode (cathode)** while the patient holds a second **reference electrode (anode)** in a hand to complete electric circuit. The treatment electrode (active surface 1,5 mm2) is applied for 2–3 seconds in one spot, then proceeding approx. 1,5 cm to another point. About 20 points are treated per one session. Frequency of treatment sessions is individual for each patient.

Attraction of extracellular and intracellular positive ions (Na+, Ca2+, K+, H+) to the treatment electrode (cathode) leads to local changes in tissue microenvironment resulting in positive treatment effects.

Indications

Rebox electrotherapy is used by physiotherapists, rehabilitation providers, general practitioners, orthopedists, algesiologists, neurologists and sport-medicine providers. The devices are also used by patients themselves in homecare treatment. The most frequent

applications include back pain, epicondylitis, sprained ankle, torticollis, knee ligament damage and other.

Acute and chronic pain

One of the main causes of pain is local acidosis due to inflammation and ischemic processes. Rebox is effective in immediate pain relief by correction of local acidosis (phenomena called *Transcutaneous Correction of Local Acidosis - TCLA*).

Immobility and hypertonia

Local changes in calcium ions (Ca2+) concentrations cause myorelaxation (decrease of muscular hypertonia and spasm) and significant improvement in range of motion.

Oedema

Rebox currents improve circulation of blood and lymphatic fluid (mainly due to Na+ movement) leading to antioedematous effect in affected area.

Neurological disorders

Rebox therapy is used in rehabilitation of after-stroke conditions, Multiple Sclerosis, phantom pain, Parkinson disease and other.

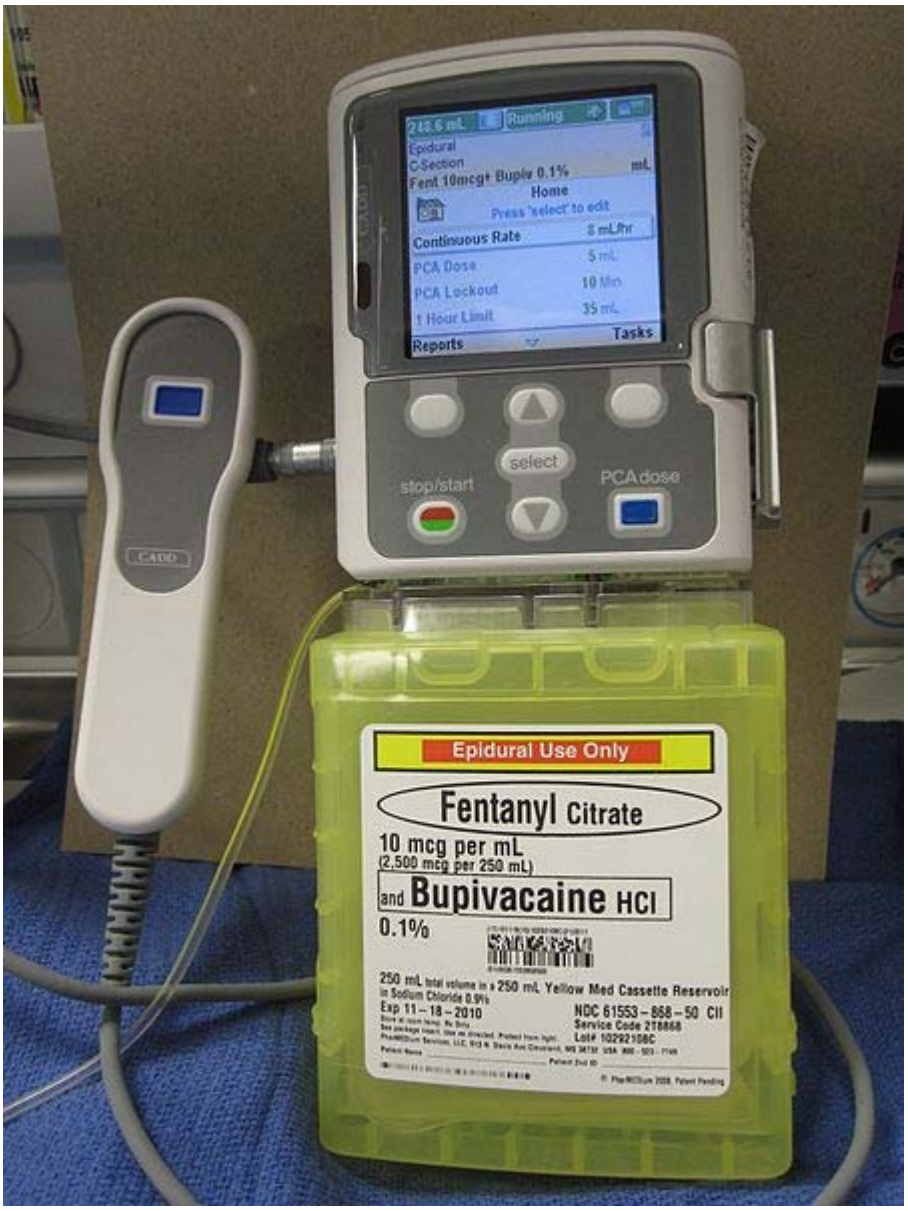
Healing processes

The method facilitates healing processes, this effect is mostly visible in wounds after surgery.

Diagnostic value

Tissue electric microcharacteristics can be visualized by the Rebox devices. The physiological curve differs from pathological situations and is specific for variety of disorders. This diagnostic value is helpful for monitoring of effectiveness and progress of treatment.

Patient-controlled analgesia



A patient-controlled analgesia infusion pump, configured for epidural administration of fentanyl and bupivacaine for postoperative analgesia

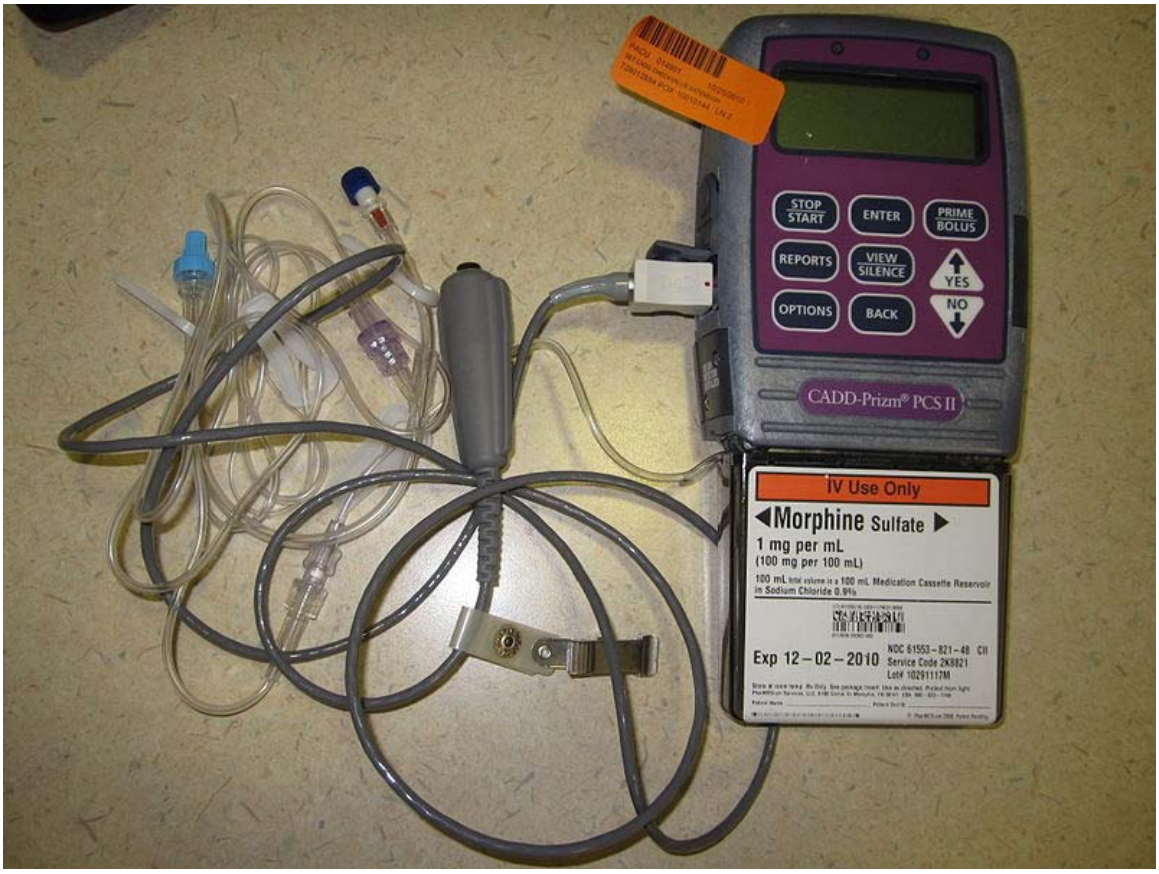
Patient-controlled analgesia (**PCA**) is any method of allowing a person in pain to administer their own pain relief. The infusion is programmable by the prescriber. If it is programmed and functioning as intended, the machine is unlikely to deliver an overdose of medication.

Routes of administration

Oral

The most common form of patient-controlled analgesia is self-administration of oral over-the-counter or prescription painkillers. For example, if a headache does not resolve with a small dose of an oral analgesic, more may be taken. As pain is a combination of tissue damage and emotional state, being in control means reducing the emotional component of pain.

Intravenous



A patient-controlled analgesia infusion pump, configured for intravenous administration of morphine for postoperative analgesia

In a hospital setting, a PCA refers to an electronically controlled infusion pump that delivers an amount of intravenous analgesic (usually an opioid) that is set by the patient. PCA can be used for both acute and chronic pain patients. It is commonly used for post-operative pain management, and for end-stage cancer patients.

Narcotics are the most common analgesics administered through PCAs. It is important for caregivers to monitor patients for the first two to twenty four hours to ensure they are using the device properly.

Epidural

Patient-controlled epidural analgesia (PCEA) is a related term describing the patient-controlled administration of analgesic medicine in the epidural space, by way of intermittent boluses or infusion pumps. This can be used by women in labour, terminally ill cancer patients or to manage post-operative pain.

Inhaled

In 1968, Robert Wexler of Abbott Laboratories developed the Analgizer, a disposable inhaler that allowed the self-administration of methoxyflurane vapor in air for analgesia. The Analgizer consisted of a polyethylene cylinder 5 inches in length and 1 inch in diameter with a 1 inch long mouthpiece. The device contained a rolled wick of polypropylene felt which held 15 milliliters of methoxyflurane. Because of the simplicity of the Analgizer and the pharmacological characteristics of methoxyflurane, it was easy for patients to self-administer the drug and rapidly achieve a level of conscious analgesia which could be maintained and adjusted as necessary over a period of time lasting from a few minutes to several hours. The 15 milliliter supply of methoxyflurane would typically last for two to three hours, during which time the user would often be partly amnesic to the sense of pain; the device could be refilled if necessary. The Analgizer was found to be safe, effective, and simple to administer in obstetric patients during childbirth, as well as for patients with bone fractures and joint dislocations, and for dressing changes on burn patients. When used for labor analgesia, the Analgizer allows labor to progress normally and with no apparent adverse effect on Apgar scores. All vital signs remain normal in obstetric patients, newborns, and injured patients. The Analgizer was widely utilized for analgesia and sedation until the early 1970s, in a manner that foreshadowed the patient-controlled analgesia infusion pumps of today. The Analgizer inhaler was withdrawn in 1974, but use of methoxyflurane as a sedative and analgesic continues in Australia and New Zealand in the form of the Penthrox inhaler.

Transcutaneous

Transcutaneous delivery systems, including iontophoretic systems, are available. These are popular for administration of opioids such as fentanyl, or local anesthetics such as lidocaine. Iontocaine is one example of such a system.

Advantages and disadvantages

Advantages of the use of Patient Controlled Analgesia include the lack of waiting time for patients requiring pain medication before a caregiver can increase the dosage of medication. In this way, the patient spends less time in pain and as a corollary to this, patients tend to use less medication than in cases in which medication is given according to a set schedule. Disadvantages include the possibility that the button can accidentally pressed, delivering an unneeded increase in the dosage of the medication. Many newer systems have mechanisms to prevent this. Also, if a PCA device is not programed properly for a patient it can result in an under-dose or overdose in a medicine.

History

The PCA pump was developed and introduced by Philip H. Sechzer in the late 1960s and described in 1971.