# Use and abuse of over-the-counter analgesic agents

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Pain and discomfort in everyday life are often treated with over-the-counter (OTC) analgesic medications. These drugs are remarkably safe, but serious side effects can occur. Up to 70% of the population in Western countries uses analgesics regularly, primarily for headaches, other specific pains and febrile illness. It is not known whether the patterns of use are consistent with good pain management practices. OTC analgesics are also widely used to treat dysphoric mood states and sleep disturbances, and high levels of OTC analgesic medication use are associated with psychiatric illness, particularly depressive symptoms, and the use of alcohol, nicotine and caffeine. More than 4 g per day of acetylsalicylic acid (ASA) or acetaminophen over long periods is considered abuse. People using excessive amounts of OTC analgesics may need more effective treatments for chronic pain, depression or dysthymia. The possibility that these drugs have subtle reinforcing properties needs to be investigated. Certainly phenacetin, which was taken off the market in the 1970s, had intoxicating effects. A better understanding of patterns of use is needed to determine the extent of problem use of OTC analgesics, and whether health could be improved by educating people about the appropriate use of these drugs.

Dans la vie quotidienne, on traite souvent les douleurs et l'inconfort au moyen d'analgésiques en vente libre. Ces médicaments sont d'une sûreté remarquable, mais ils peuvent avoir de sérieux effets secondaires. Jusqu'à 70 % des habitants des pays occidentaux utilisent régulièrement des analgésiques, surtout contre les céphalées, d'autres douleurs précises et la fièvre. On ne sait pas si les tendances de l'utilisation correspondent à de bonnes pratiques de gestion de la douleur. Les analgésiques en vente libre sont aussi très répandus pour traiter les humeurs dysphoriques et les troubles du sommeil, et l'on a établi un lien entre des taux élevés de consommation d'analgésiques en vente libre et certaines maladies psychiatriques, en particulier les symptômes dépressifs, ainsi que la consommation d'alcool, de nicotine et de caféine. On considère comme de l'abus la consommation de plus de 4 g par jour d'acide acétylsalicylique ou d'acétaminophène pendant des périodes prolongées. Les personnes qui consomment des quantités excessives d'analgésiques en vente libre peuvent avoir besoin de traitements plus énergiques contre la douleur chronique, la dépression ou la dysthymie. Il faut étudier la possibilité que ces médicaments aient des caractéristiques subtiles de renforcement. La phénacétine, qui a été retirée du marché au cours des années 1970, avait certainement des effets intoxicants. Il faut mieux comprendre les tendances de la consommation afin de déterminer l'ampleur de la consommation problématique d'analgésiques en vente libre et de savoir si l'on pourrait améliorer la santé en éduquant les gens au sujet de la bonne façon de consommer ces médicaments.

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Medical subject headings: acetaminophen; analgesics; anti-inflammatory agents, non-steroidal; aspirin; caffeine; codeine; cyclooxygenase inhibitors; drug combinations; drugs, nonprescription; headache; ibuprofen; kidney failure; liver failure; overdose; pain; pharmacokinetics; phenacetin; substance abuse

*J Psychiatry Neurosci* 1998;23(1):13-34.

Submitted Feb 28, 1997
Revised Sept. 15, 1997
Accepted Sept. 17, 1997

## Introduction

In 1985 in the United States, 4 billion work days were lost because of pain, amounting to about 23 days per person for full-time, part-time and at-home workers. For those employed full time, 550 million days were lost. Based on an average income of $23 000 per year, losses as a direct result of pain are estimated at $55 billion.[1] In Canada, headaches lead to time away from work and impairment of functioning in more than 34% of the population.[2] Some of those with pain consult a physician: pain, in fact, is the most common reason for medical consultation. Many more simply buy an over-the-counter (OTC) medication and treat themselves. Others do both — one study found that 37% of patients who received a prescription for analgesics were taking an OTC medication for pain concomitantly.[3]

Eighty-five percent of all analgesics are sold over the counter,[4] and pain-relievers as a group post the highest sales among OTC drugs.[5,6] In pharmacies in Montreal there are over 60 OTC analgesic formulations, revolving around 3 drugs: acetaminophen, acetylsalicylic acid (ASA) and ibuprofen. It has been estimated that 20–30 billion tablets of ASA are taken each year in the United States.[7] Over the past 15 to 20 years, approximately 187 billion tablets of acetaminophen have been consumed by 170 million US adults, for an average of 9–13 billion annually,[8] or 50–70 tablets per person per year. Current use is higher than these figures indicate — acetaminophen has grown as a proportion of OTC analgesics used during this period, and the use of ASA has fallen concomitantly.[9] Advertising encourages use, as exemplified by a sharp increase in sales of ibuprofen immediately after it became an OTC agent in 1986.[10] In 1972 in Australia, 1% of all spending on television, radio and newspaper advertising, excluding posters and billboards in pharmacies and grocery stores, went to promote OTC analgesics.[11] Former US Federal Communications Commissioner Nicholas Johnson once proposed a ban on OTC drug commercials, arguing that they are no different from a "pusher." He stated, "We've got a drug problem in America. It's called television."[12,13]

In this review, the pharmacology and toxicology of OTC analgesics are covered briefly in the first section. The next section discusses the epidemiology of OTC analgesic use, beginning with historical data on phenacetin, which was withdrawn from the market in most Western countries in the early 1970s. Following this, the role of OTC analgesics in pain management, the abuse of phenacetin and the much more equivocal, but suggestive, evidence for abuse or misuse of currently available OTC analgesics are discussed. The final sections deal with the possibility that OTC analgesics or analgesic mixtures have subtle reinforcing effects.

## The drugs and their pharmacological actions

The drugs considered here share, to varying degrees, *anti-inflammatory, antipyretic* and *analgesic* actions, and are commonly described as nonsteroidal anti-inflammatory drugs (NSAIDs). The prototypical agent, ASA, was introduced by Bayer as Aspirin in 1899. Acetaminophen was synthesized in 1893, but was not widely used until the 1950s.[14] These are currently the 2 most commonly used OTC pain medications. There is a debate about whether acetaminophen should be classified as an NSAID since it lacks anti-inflammatory effects. However, as discussed below, its pharmacological actions are similar to other NSAIDs, and it is subsumed under that term in Goodman and Gilman's textbook.[14] In the past 30 years many other NSAIDs have been introduced, most of which are used to control inflammation, rheumatic disease and menstrual pain, and most of which are available only with a prescription. Ibuprofen, which is available over the counter in many Western countries, including Canada, is the exception. In the near future, other prescription NSAIDs will likely become available over the counter — naproxen, for example, recently became an OTC agent in the United States.

A large proportion of OTC analgesics contain an NSAID combined with a variety of other agents. The most common adjunctive agent in Canada is 30–60 mg of caffeine per tablet (a cup of coffee contains 50–150 mg of caffeine, and a can of Coca-Cola about 45 mg). Caffeine potentiates the analgesic actions of many classes of analgesics.[15] Tablets sold for dysmenorrhea contain cinnamedrine (a sympathomimetic with effects like ephedrine), or pamabron (a mild diuretic) and pyrilamine maleate (an antihistamine). Some cold medications contain ASA or acetaminophen, along with vitamin C, a decongestant, an antihistamine or some combination of these. Preparations for back problems combine ASA or acetaminophen with methocarbamol or chlorzoxone, mus-

cle relaxants with nonspecific sedative action. Canadian law allows 8 mg of codeine per tablet in OTC preparations, and many of the above preparations are available with or without codeine.

*Mechanisms of action*

NSAIDs act by reversibly or irreversibly inhibiting cyclooxygenase 1 and 2 (COX 1 and COX 2), enzymes involved in the synthesis of unstable precursors of prostaglandins. Prostaglandins play a role in a host of normal physiological processes, both in the periphery and the central nervous system (CNS), and COX 1 is expressed constitutively in many tissues. COX 2 is induced in inflamed tissues, producing redness by dilating blood vessels, swelling by accumulation of fluid in the extracellular spaces, and pain by sensitizing nerve endings.[16] The analgesic actions of NSAIDs are due, at least in part, to their ability to reduce inflammation by inhibiting COX 2. However, there are additional analgesic actions, exemplified by acetaminophen, which is a good analgesic and anti-pyretic but a weak anti-inflammatory agent. These properties may be due in part to the low affinity acetaminophen has for COX in environments that are high in peroxide, such as occurs in inflamed tissues.[14] Acetaminophen is thought to produce analgesia both in the spinal cord and at higher levels of the CNS.[17–21] Other NSAIDs also act in the CNS to produce analgesia to varying degrees. Patients with rheumatic disease develop distinct preferences for particular agents,[22] but whether this is due to differences in efficacy at the various sites of action is not known. ASA may also reduce the incidence of myocardial infarction and occlusive stroke by irreversible inhibition of COX 1 in platelets, which reduces their tendency to clot.[14]

*Toxicity*

NSAIDs are efficacious and have a wide margin of safety. However, they do have potentially serious side effects that can occur even when they are taken in appropriate doses, and the impetus for the development of new NSAIDs has arisen from the desire to produce agents with reduced potential for adverse effects. The most common side effects are gastrointestinal. The inhibition of prostaglandin formation in the stomach wall can lead to inflammation, bleeding and ulceration.[14] Acetaminophen, however, does not cause gastric irritation, possibly because of its poor affinity for COX in that particular environment. One to 7 days of treatment with ASA or ibuprofen produces gastrointestinal lesions that are readily observed on endoscopy in 20%–50% of normal subjects.[7,23,24] Maximum damage to the stomach occurs within 3 days of the initiation of therapy, and then tends to improve with the development of cytoprotective mechanisms.[23] Nevertheless, in case–control studies of patients admitted to hospital it was found that long-term NSAID therapy increased the risk of gastrointestinal bleeding 10- to 30-fold.[25] The gastrointestinal effects are dose-dependent and are detectable even at doses used for prophylaxis of cardiovascular disease. For example, in a double-blind placebo-controlled study of elderly people, 100 mg of ASA per day for 12 months led to a small but statistically significant decrease in hemoglobin in those treated with ASA, and clinically significant bleeding in 3%.[26] Women consume more OTC analgesics than men (see below), but whether this contributes to anemia (which has a 2%–5% prevalence rate in women in the United States[27]) has not received attention. In 1992, the medical costs to treat the gastrointestinal side effects of NSAIDs in the United States were estimated to be $3.9 billion per year.[28]

Although acetaminophen does not cause gastrointestinal problems like the other NSAIDs, it can cause liver damage, and these effects can occur at therapeutic doses in some circumstances. Acetaminophen is metabolized in the liver, and normally 90% to 100% is recovered in the urine as sulfate and glucuronide derivatives. However, a secondary pathway metabolizes acetaminophen to a highly reactive intermediate, which is normally reduced by glutathione. If liver glutathione is depleted, hepatotoxicity can occur. People who suffer from alcoholism are at increased risk for acetaminophen-induced hepatotoxicity, because alcohol increases the tendency for acetaminophen to be metabolized by the secondary pathway, and chronic alcohol consumption depletes glutathione.[29–33] The high prevalence of alcoholism in North America makes this a significant risk. For example, the Edmonton survey found that 21% of the population reported drinking heavily at some time in their life, and 18% reported drinking more than a fifth of liquor (26 oz. or approximately 750 mL) in 1 day at least once.[34] Fasting and malnutrition also reduce glutathione availability and increase the risk for hepatotoxicity in those taking acetaminophen for persistent pain or fever.[32,35,36] This

kind of liver damage is almost always unintentional, and often goes unrecognized.

Inhibition of COX 1 in the kidney reduces renal blood flow, glomerular filtration, tubular sodium, potassium and chloride transport, and water clearance, thereby reducing overall renal function. Because of this, NSAIDs can contribute to acute renal failure in patients with congestive heart failure, hepatic cirrhosis, renal disease or hypovolemia.[14] In addition, NSAIDs can cause renal papillary necrosis (analgesic nephropathy), which can progress to end-stage renal failure. In 1974, phenacetin (acetophenetidin), a compound that is converted to acetaminophen in vivo, was taken off the Canadian market because it was believed to cause analgesic nephropathy. It was later suggested that it was not the phenacetin *per se* that led to nephrotoxicity, but an interaction between the phenacetin and ASA, with which it was usually formulated. After phenacetin was withdrawn (1968–72), disease progression in people with established analgesic nephropathy and new cases in people who had used phenacetin were apparently caused by other NSAIDs, particularly ASA.[37,38] More recent studies indicate that analgesic nephropathy can be induced by the chronic consumption of any NSAID.[4,38,39] The absolute risk of end-stage renal disease for an "abuser" of OTC analgesics is estimated to be in the same range as the risk of lung cancer for a smoker: 1.6 in 1000 people per year for those who abuse analgesics versus 2.1 in 1000 people per year for those who smoke.[38] If 10% of end-stage renal disease is attributable to NSAID use, this translates into an annual cost of $700 million in the United States.[39]

*Dosing recommendations*

The normal adult dose of ASA or acetaminophen is 0.3–1.0 g every 4–6 hours, up to a maximum of 4 g per day. Fifty mg per day of ASA is sufficient to inhibit platelet function. The OTC formulations available are sold as "regular," "extra strength," "super extra strength" and "maximum strength," containing 325, 500, 650 and 900 mg of ASA or acetaminophen, respectively. The extent to which dose recommendations are exceeded is not known. Interestingly, Wolff et al[40] found that the maximum analgesic effect of ASA occurred at 0.3 g and did not increase with increases in dose. The recommended daily maximum dose of ibuprofen is 1.6 g: OTC formulations contain 200 and 400 mg. The main effects and side effects of ibuprofen and ASA are very similar.[14]

*Overdose*

Acetaminophen, ASA and ibuprofen are all among the top 10 drugs in the United States Drug Abuse Warning Network statistics for emergency room contacts resulting from self-administered drugs, usually with evidence of suicidal intent.[41] A survey of high school students in Florida who were taking a voluntary counselling course (i.e., a highly selected, socially conscious group) found that 17% did not think that acetaminophen could be lethal, and a further 23% seriously underestimated the dose that could be fatal.[42] The authors considered this to be consistent with clinical impressions that many patients admitted for acetaminophen overdose may be making a gesture with a drug that they do not perceive to be particularly dangerous. Liver damage can be prevented or minimized if an antidote is given within 16 hours of taking the drug, but the first symptoms of overdose — gastrointestinal pain, vomiting and anorexia — sometimes do not appear for 24 hours and abnormal liver function may not be apparent for 48 hours.[14]

In the absence of suicidal intent, diagnosis of overdose with OTC analgesics is frequently delayed, with serious consequences in terms of morbidity and mortality. Patients who unintentionally overdose are older, tend to have concurrent medical problems, and have usually been taking analgesics for long periods of time. Because they have been taking the drugs for so long, they often fail to mention their consumption of OTC analgesics on admission.[43,44]

## Epidemiological studies of OTC analgesic use

*Before 1970 — the phenacetin era*

Epidemiological studies of OTC analgesic use began in the 1960s and 70s, when an epidemic of kidney failure became apparent in many Western countries. One of the causes of this epidemic was a rapid increase in consumption of OTC analgesics during the decade following World War II. Fig. 1 shows the increase in imports into Canada of ASA, phenacetin and codeine, used primarily for production of OTC analgesics, between 1946 to 1966. Note the steady *logarithmic* increase over the

20-year period. The consumption of ASA increased 4-fold to about 20 g (approximately 60 tablets) per person per year for every man, woman and child.

In the United States, Denmark and Australia, consumption doubled between the war and 1960.[45-47] Per capita consumption estimates for phenacetin in the late 1960s for selected countries are shown in Table 1. The variability in consumption is particularly striking. In addition, regional differences within countries

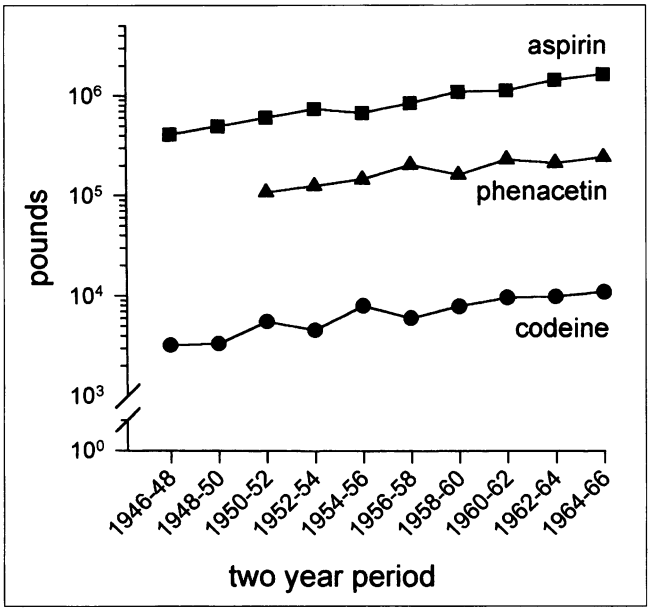


**Fig. 1: Imports of ASA (aspirin), phenacetin and codeine into Canada for the 20-year period following World War II, when none of these agents were produced domestically. In 1964–66, 1 646 666 pounds of ASA were imported, equivalent to about 20 g per year for every man, woman and child. Popular formulations contained phenacetin and ASA in a 1:2 or 1:3 ratio; about half of the ASA must have been used in a preparation not containing phenacetin. Data from Gault et al.[45]**

**Table 1: Per capita consumption of phenacetin in the late 1960s and early 1970s for various countries. ***

| Country | Per capita phenacetin consumption, g/yr |
|---|---|
| Australia | 40 |
| Denmark | 25 |
| Switzerland | 23 |
| South Africa | 12.5 |
| Scotland | 12 |
| United States | 10 |
| England and Wales | 8 |
| Canada | 6–7 |

*The consumption of phenacetin in Canada is consistent with the levels shown in Fig. 1. Data from Murray,[47] except data from Denmark, which is from Gault et al.[45]

of up to 5- or 6-fold were not uncommon.[46,47] For example, in Queensland, Austrialia, between 1971 and 1976, 16% of women and 11% of men reported taking an "analgesic powder" at least daily, whereas in Western Australia, the figures were only 3% for both men and women.[39] Similar regional differences occurred in rates of analgesic nephropathy. Ten percent of end-stage renal disease in patients in Berlin was due to analgesic nephropathy, whereas in Bayern, Germany, it was only 2%.[4] These data indicate that there are strong cultural influences on the extent of OTC analgesic use. However, the negative correlation between the prevalence of analgesic nephropathy and of renal failure of "unknown etiology"[38] suggests that some of the national and regional fluctuations reflect differences in diagnostic criteria. The prevalence of analgesic nephropathy in Britain was related not to absolute amounts of NSAIDs sold, but to the sales of formulations containing a mixture of phenacetin, ASA, caffeine and sometimes codeine.[38,48]

Patients with analgesic nephropathy presented a very consistent picture.[4,11,38,46,48-51] They were most often women between 45 and 60 years old with extensive histories of gastrointestinal ulceration and bleeding, indicating continued use of the drugs despite abdominal discomfort. Estimates of lifetime intake of phenacetin and ASA ranged from 5 kg to well over 20 kg. Five kg is equivalent to 4 g per day for 3 years, and most studies define 4 g per day of an NSAID preparation as abuse. Headaches were the primary reason for using OTC analgesics in most studies, and psychiatric problems, including depression, alcohol and other substance abuse, and anxiety, were observed in over 50% of patients. In one of the few studies involving men, of 500 consecutive patients in a Canadian veteran's hospital, 32 (6.4%) were abusing analgesics.[45] Ten of these were chronic alcoholics, 13 were depressed and 6 had chronic anxiety.

### *Early population surveys*

Studies of analgesic nephropathy were followed by surveys to determine the patterns of use of OTC analgesics. In a small town in Victoria, Australia, in 1975, 28% of the population admitted to taking at least 1 analgesic per week.[52] The range was from 1 to 56 doses per week, with a median intake of 1.9 doses per week in those who took any analgesic. Screening of urine samples for salicylate indicated a strong positive cor-

relation between the proportion of positive samples and reported intake, but 10% of those who denied using analgesics had a positive result. Intake by women was nearly double that by men, although the sex difference was less pronounced when only heavy users were considered. There was no relation between social class, marital status, tea, coffee or nicotine consumption and analgesic intake in this study. The reasons for use were predominantly headaches or other pain, but 6.4% used OTC analgesics "to pick me up," for "nerves," and so on. The distribution of the amount used was a smooth exponential decay curve, with many people using small quantities and progressively fewer people using large amounts, similar to the Lederman curves for alcohol consumption. This indicates that users form a continuum, with no bulge suggesting a different population at the high end of consumption. Similarly, in Sydney, Australia, 14.7% of women and 7.9% of men took ASA (usually combined with phenacetin) daily.[53] Predictors of consumption were similar to the study above, and most subjects were taking NSAIDs for pain or physical discomfort — 41% reported that they took a pill for headaches. However, some people reported taking them for less well-defined conditions that suggest use to alleviate psychological distress. "Nerves," "tension," "out of habit" and "to cope with family" together accounted for 31% of use in this sample. "Nerves" alone accounted for 51% of use in women under 40 years of age.

A prospective study offering screening for kidney disease or diabetes to 13 000 working women was begun in Switzerland in 1968.[54] Urine screening for the phenacetin metabolite acetaminophen identified 623 women (4.8%) with normal kidney and liver function and positive samples on 2 occasions. However, compared with a matched control group, these women's kidney function deteriorated over the 7-year follow-up period. A subsample of these women underwent testing with a German equivalent of the Minnesota Multiphasic Personality Inventory in 1972 and 1975.[50] Those with high urinary levels of phenacetin metabolites had more physical and autonomic complaints, more "ill-humour and lability of mood tinged with general depression," anxiety and apathy, as well as less self-reliance. At the 1975 follow-up, the psychological status of those in the control group had improved, whereas those still taking analgesic preparations remained "depressive and emotionally unstable."

Bush and Rabin[6] did a secondary analysis of data collected in 1968–69 in Baltimore as part of an international study funded by the World Health Organization (WHO) of prescription and nonprescription drug use. Twenty-four percent of the population had used an OTC medication within the previous 2 days, and, of these, 82% had used an analgesic. Overall, there was a positive correlation between morbidity and use of OTC medications, but 25% of those using an OTC analgesic in the previous 2 days reported no bed rest or reduced activity, no acute or chronic illness or impairment, and no other health problem. This study found that levels of OTC drug use were higher in the 2 areas of the United States surveyed than in the 6 other countries that participated in the study. Overall, living in an urban environment, being a woman, having a higher level of education, being older and having increased levels of morbidity predicted greater use of OTC drugs.[5]

### *Post-phenacetin epidemiology*

Since the withdrawal of analgesic mixtures containing phenacetin, the data on the use of OTC analgesics are patchy. A study of medications consumed by persons 65 and over in the United States found that analgesics were the most commonly used drugs.[55] Whereas 10.4% of the sample had used prescription analgesics, 38.4% had used OTC analgesics at least once in the previous 2 weeks. Another study, involving 2565 women between the ages of 45 to 55 in Massachusetts, found that 85% of the women used OTC analgesics, and 8% used them daily. Women who had been prescribed an NSAID used OTC analgesics more often than other women. The "mixed users" were not substituting one for the other, but, rather, using them both. These women were less likely to be married, had fewer children, and had less that 12 years of education.[56]

A recent survey of the use of prescription and OTC drugs in Norway involving 19 137 people found that 28% of women and 13% of men had taken analgesics within the previous 2 weeks.[57] As illustrated in Fig. 2, analgesic use by women increased rapidly at the onset of menstruation. However, the sex difference was not fully explained by menstrual discomfort; when women who reported menstrual pain were excluded, the sex deferential was only slightly reduced. It is clear from other studies that women take more pain-relievers than men.[3–6,11,47,58,59] The most prominent predictor of analgesic use for both women and men was headaches,

followed by febrile illness and back pain. Coffee consumption was also significantly related to increased probability of analgesic use, as was daily smoking. In contrast to the earlier studies and the Massachusetts study referred to above, having a higher level of education was associated with increased probability of use. After pain or illness, the significant predictors of analgesic use for women were self-reported depressed mood and premenstrual distress, whereas for men the predictors were sleep problems, low level of physical activity and being married.

*Use of OTC analgesics in Canada*

In the 1994–95 National Population Health Survey,[60] subjects were asked if they had used "pain relievers or anti-inflammatory" agents (referred to as NSAIDs in the following discussion) within the previous month. Unfortunately, the questionnaire did not separate prescription NSAIDs from OTC analgesic agents or ask about frequency of use. Nevertheless, the same themes as those in studies going back to the phenacetin era arose: higher levels of use by women and an association between use and depression and life stress. Sixty-six percent of women and 55.6% of men (overall 61.0%) reported that they had used an NSAID at least once in the previous month. A breakdown of use by province is shown in Fig. 3. There is considerable variability, again suggesting strong cultural influences on the use of these drugs. Fifty-eight percent of those reporting no chronic functional limitation due to pain had used an NSAID, and the figure rose systematically with degree of limitation to 84% in those reporting that most activities were limited by pain. The implication is that 58% of those who reported taking analgesics or anti-inflammatory agents in the previous month did not report functional limitation due to pain. Some of these people will have had acute, time-limited problems for which the drugs were used, but, given the data from earlier studies, the sample probably included people who were using OTC analgesics for other reasons. In fact, 75% of the respondents who scored high on questions relating to depressed mood (90% or greater probability of meeting diagnostic criteria for major depression), or of those who had used antidepressant medication in the past month, had used NSAIDs. There was also a systematic increase in the probability of using NSAIDs with increasing life stress (Fig. 4).

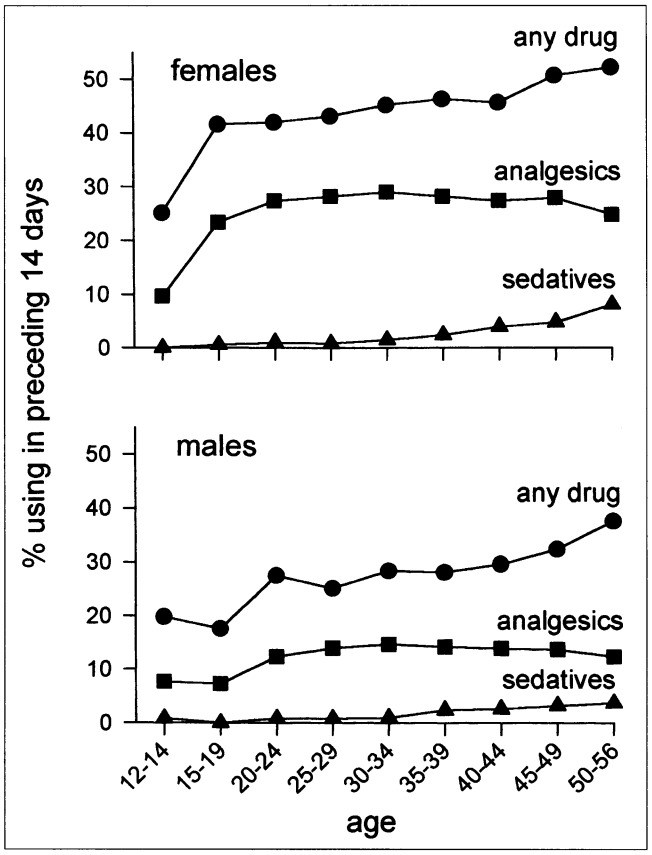


**Fig. 2: Percentage of the population using analgesics (prescription and OTC combined), by age, in the preceding 14 days in Norway in 1992. Use of analgesics by women more than doubles around the age of menarche, and analgesics account for more than half of total medication intake by women until after menopause. The use of sedatives is infrequent until after the age of 35. Data from Ahonen et al.[10]**

Another Canadian survey focused on people who suffer from headaches.[2] From the sample, it was estimated that 3.2 million or 16.5% of the population suffer from migraine, and 5.8 million or 29.5% of the population suffer from tension headaches. The mean frequency was 21 episodes per year for both types of headaches, and in 50% of the patients suffering from migraine and 18% of those suffering from tension headaches the pain caused them to discontinue normal activities. Only 64% of the people with migraine and 45% with tension-type headaches had consulted a physician about their headaches. Although 44% and 24%, respectively, had used prescription medications, 91% and 90% had used OTC medications. Both groups reported using medication 3 times a week on average, most often ASA or acetaminophen alone or with caffeine and codeine. Similarly, a survey of non-

prescription drug use in Winnipeg found that 41% of a random sample of adults had used an OTC analgesic in the previous 2 weeks.[61]

*Summary*

Clearly, the OTC analgesics are very important agents for managing the aches and pains of everyday life, and most individuals use them intermittently, with headaches being the single most common reason for use. During the phenacetin era, heavy use of OTC analgesics was strongly associated with women and psychological distress, particularly depressive symptoms. Current Canadian use of OTC analgesics is also associated with these factors. The implication is that, in a psychiatric context, the vast majority of patients with depressive or anxiety disorders probably use OTC analgesics, and some of them take high levels of these drugs.

The withdrawal of phenacetin does not appear to have led to marked decreases in OTC analgesic use. For example, in the prospective study of working women in Switzerland, discussed above, the urine samples of 4.8% tested positive for phenacetin on 2 separate occasions. Assuming men were using phenacetin half as

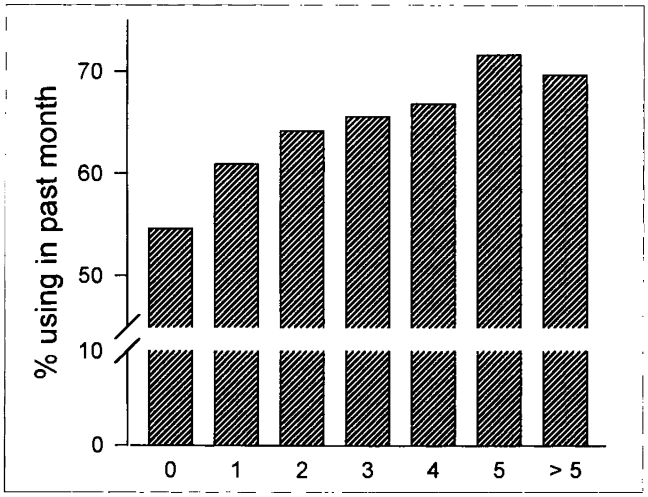


**Fig. 4: Percentage of population of Canada using an analgesic or anti-inflammatory agent in the past month, by derived chronic stress score (which takes into account family, job and life stress). Data from Statistics Canada.[60]**

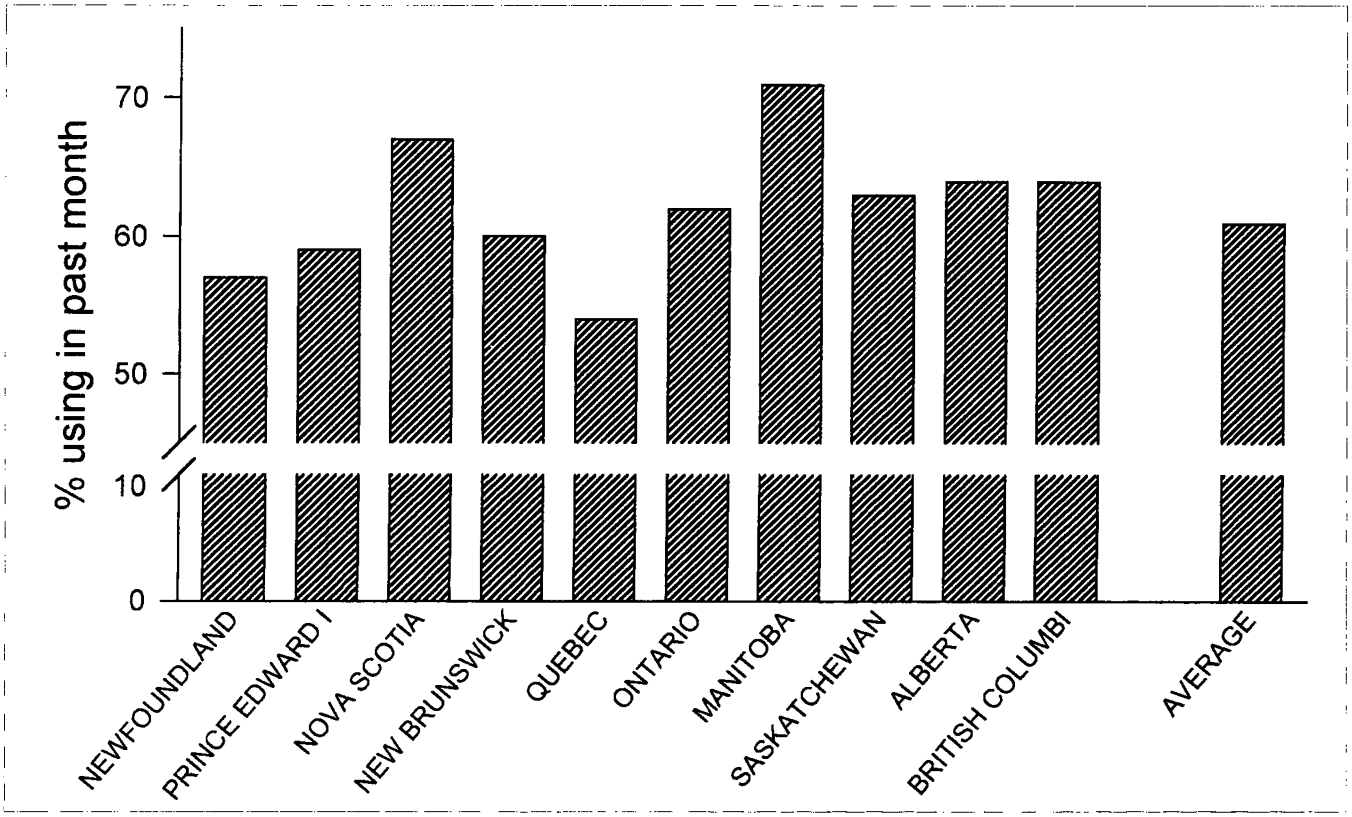


**Fig. 3: Estimated percentage of the Canadian population reporting the use of an analgesic or anti-inflammatory agent at least once in the previous month, by province. Data from Statistics Canada.[60]**

much, a ball park estimate of positive urine samples in the population would be about 3.5%. Consider the Canadian data described above. If only headache sufferers (46% of the population) used OTC analgesics, averaging 3 doses per week, and if metabolites could be detected in urine samples for 12 hours after any given dose, then 21% of samples would test positive at any given time. Assuming random and equal distribution of use, it would be expected that 4.6% would have positive results on 2 separate occasions. The actual proportion of positive urine samples would be less if there was a tendency for people to take much more than 3 doses per week, or for all 3 doses to be taken on 1 day. Considering these factors, if the proportion of positive samples is adjusted downward by a factor of 2, that still means that 1% (46% × 2.3%) of the population would test positive for OTC analgesics taken for headache alone. The surveys discussed above suggest that headaches account for 30%–40% of the use of OTC analgesics. Thus, between 2.5% and 3.3% of Canadian adults would be expected to test positive for OTC analgesics at any given time. This is remarkably close to the estimate for phenacetin-positive urine samples in Switzerland.

## Conceptual frameworks for OTC analgesic use

The data described above suggest 2 broad uses for OTC analgesics. The first is to alleviate the aches and pains of everyday life. From this perspective, optimal and safe use is a pain management issue. The second is to treat stress, anxiety, depression and sleep disturbances. This could be considered abuse, since OTC analgesics are not recommended to treat these conditions. In addition, some phenacetin users probably met the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) criteria for substance abuse: "a maladaptive pattern of substance use, leading to clinically significant impairment or distress."[62] This may also be the case for some users of currently available agents.

## Pain management

### *Analgesic use in clinical samples*

Whereas the surveys discussed above give the impression that the vast majority of Western populations are popping pills for every minor discomfort, studies in clinical populations suggest a different picture. It is clear that there are serious problems in pain management in hospitals. Marks and Sachar[63] described the gross underuse of analgesic drugs by patients in hospital. This problem has persisted. A survey of patients in McGill University teaching hospitals in 1986–87[64] indicated that nearly half of patients with moderate or severe pain had not received any analgesic medication in the previous 24 hours. Low levels of analgesic use persisted after discharge: during follow-up interviews 3 and 6 months later, about 60% of those who had reported pain when they were in hospital still had pain, and they reported that the pain interfered significantly with their ability to function. Surprisingly, less than half of those who reported moderate to severe pain had used any analgesic, prescription or OTC, in the 24–hour period before the interview. Similarly, 50% of a sample of elderly people living in the community in Winnipeg had daily pain.[65] Less than half of those with pain were taking analgesics, although those who did reported significant pain relief. Effective pain management has been shown to reduce morbidity in patients who have undergone surgery,[66] and it may reduce morbidity in the general population as well.

The reason for the discrepancies between clinical studies and population surveys is not clear. It may be that when a patient is not given a prescription for pain medication or advice regarding OTC preparations, the patient believes that analgesics are contraindicated. Another reason may relate to the fact that the studies of underuse involve patients with chronic or recurring pain conditions. This group may fear "addiction" to analgesics, or worry about saving something for when the pain worsens. Our studies using patient-controlled analgesia (PCA),[66,67] which allows patients to administer their own analgesic drugs intravenously as needed, indicate that self-management of pain is not easy. Intensive coaching and support is necessary for effective PCA. Patients have a tendency to wait until the pain is severe to administer medication, rather than administering the medication as soon as the pain starts to return; this seems to be based on fear of addiction to analgesics. Anecdotal information supports the notion that most people do not use either prescription or OTC analgesics in an optimal fashion. For example, when a person who says "I'm going to have a terrible afternoon; I've got one of my headaches," is asked what they have done

for the pain, the answer is usually "Nothing — I can still bear it." This suggests that taking an analgesic is regarded negatively. Pain management principles would dictate taking medication in an effective dose as early as possible after the onset of pain.[68]

*The costs of inadequately managed pain*

Virtually everyone has experienced a headache, sore back, menstrual cramps, etc., while having to cope with school, job or family. The sales figures for OTC analgesics indicate that a very large proportion of people regularly treat themselves to relieve pain and discomfort. For those whose discomfort is time-limited, this is a reasonable strategy to counteract the direct effects of pain, and the consumption of OTC analgesics suggests that they are, in general, perceived as highly efficacious. However, the statistics for time lost from work because of pain — estimated at 23 days per person per year in the United States[1] — indicate that there is considerable residual pain. The use of readily available OTC analgesics may not be optimal, and more appropriate use might be achieved with education programs directed at both the public and at health care personnel.

In addition to those who have time-limited problems, there are a large number of people who suffer recurrent or continuous pain. For these people, the costs of functional limitation, reduced quality of life and health care are considerable. By the time those with chronic pain conditions seek specialized pain treatment services, they may already be abusing both prescription and OTC medications. For example, in a group of patients at a headache clinic, the mean number of tablets or suppositories taken per week was 34.6 (range 7 to 128), reflecting an intake of 5.8 (range 1 to 14) different pharmacological agents simultaneously.[69]

In addition to their direct costs, chronic pain and functional limitations result in a 3- to 5-fold increased risk of depression.[70–73] There is also evidence indicating that depression may predispose a person to musculoskeletal pain[74] or migraine.[75]

The literature on pain supports the notion that individuals with pain that is difficult to treat are perceived negatively by health care professionals, and this may lead to unsupervised overuse of OTC medications. People in pain-management programs for whom treatment fails tend to vote with their feet, and the dropout rates for studies of treatment efficacy are frequently over 50%, particularly if follow-up is longer than 3 months.[76] New treatments for chronic pain go in and out of fashion, and in many cases the initial claims of efficacy are not borne out with wider use. In fact, Sherman et al[77] reported that, at best, 30% of patients improved with treatments for phantom limb pain, and that the more any given treatment had been used, the lower it was rated in terms of efficacy. Moreover, patients whose pain does not improve with treatment are regarded negatively by practitioners (e.g., "my treatments are successful, it's these patients who are the failures").[76] In hospitals, patients who have pain and do not cope well with it are regarded as demanding and unpopular by the nursing staff.[78] The negative perception of patients with analgesic nephropathy and users of large quantities of OTC analgesics described above may be due, at least in part, to the fact that some of these people suffer from chronic painful conditions that have not responded to treatment.

*Summary*

We do not know the extent to which chronic pain can be managed more effectively at an earlier stage with rational use of OTC preparations. Surveys have concentrated on either the burden of pain conditions in the community or on the total quantity of medications used, and not on patterns of use. It is also not known whether individuals treating chronic pain conditions with OTC preparations could benefit from either stronger analgesics or low doses of antidepressant drugs under appropriate medical supervision. Since the surveys of OTC analgesic use discussed above indicate a relationship between depressive symptoms and use of OTC analgesics, it is possible that there are many regular users of OTC analgesics who need to be evaluated for depression or dysthymia. Conversely, those being treated for depression or dysthymia need to be asked explicitly about pain and analgesic use.

## Abuse and misuse of analgesics

The use of OTC analgesics to treat problems other than pain or fever was first drawn to our attention 20 years ago when, in the course of a coffee-room conversation, a university professor stated, "Of course I take Tylenol when I get up in the morning: it makes me feel better." Since then a number of other instances of this use of NSAIDs have been observed. A 14-year-old high

school student was recently overheard advising a friend who had suffered a disappointment (tickets to a rock concert were sold out) to "take a Tylenol." It is apparent from the foregoing discussion that persistent heavy use of OTC analgesics may arise from treatment of chronic pain, but regular morning doses and use to treat disappointments are hard to explain in the context of pain. This type of use suggests that some individuals use OTC analgesics to treat psychological problems and stress. Certainly, phenacetin appears to have positive reinforcing properties or mood-enhancing effects associated with a clear pattern of substance abuse or dependence. For other OTC analgesics, there is much less information, primarily because the drugs are much safer, and problem use is not as easily identified.

The first problem is arriving at a definition of what constitutes abuse or misuse. In the following, 3 different kinds of use are discussed. The first is persisting use of higher-than-recommended doses without medical advice. The second is use to treat symptoms for which the drug is not indicated. The third is use to produce intoxication. The sections below discuss the abuse or misuse of OTC analgesics using these definitions. The first 2 sections cover phenacetin and currently available OTC analgesics. The last section focuses on headaches.

### *Abuse of phenacetin*

The data on phenacetin clearly indicate that heavy users could be described as drug-dependent according to the DSM criteria. In the 1960s many clinicians commented on the fact that patients with analgesic nephropathy frequently denied taking analgesics, even when they knew that the drugs were responsible for their condition.[38,46,79–81] For example, urine samples from 81% of patients with progressive analgesic nephropathy tested positive for phenacetin metabolites (i.e., acetaminophen).[82] All of these patients denied taking analgesics, and admitted use only when confronted with the test results. Similarly, just under half of a group of women outpatients with various complaints, the most common being headache, reported occasional use of acetaminophen or analgesic agents containing phenacetin.[83] Urine tests for acetaminophen were positive in 10% of women. In these women, there was a *negative* correlation between reported consumption and acetaminophen concentration in the urine, indicating systematic under-reporting of their drug intake. As noted above, in a random sample of the population in a small Australian town, there was a correlation between the reported consumption of OTC analgesics and the probability of a positive urine test for salicylates.[52] However, about 10% of urine samples from professed nonusers also tested positive. Denial of use can lead to misdiagnosis of medical problems caused by analgesic abuse.[84]

Anecdotal descriptions of use are even more suggestive of compulsive use of phenacetin. From interviews of patients with analgesic nephropathy, Murray[48] reported that the stated reasons for use included both stimulant and sedative effects: "they give me a lift" or "calm me down." The patients also reported euphoriant effects: "an Askit is heaven, Doctor." A chemist reported that when supplies of one woman's favourite powder ran out "she would get like a wreck," and a man described his wife as "like a mad thing without a Beechams." Some chemists refused to supply the drugs to certain people, and so patients sent others to obtain their favourite preparation. Murray also found that the families of many patients opposed their drug use and would hide or destroy their supplies. A study of Swedish factory workers found that taking "Hjorton's powders" 10 to 12 times a day was not unheard of, and they were offered to coworkers in the same way as cigarettes or snuff were shared.[79] Older employees at the factory sent apprentices to buy powders and tipped them with a powder. The workers were hostile to researchers asking questions concerning their use of powders, and it was difficult to obtain an accurate estimate of daily intake. In some sectors of the factory the questionnaires were publicly burned.

As stated earlier, patients with analgesic nephropathy are not perceived positively. They have been characterized as "60-year-old disappointed and depressed females with a chronic headache" [sic], and the fact that they continue to "demand" analgesics has been discussed in relation to drug addiction.[85] In a study of 51 patients with analgesic nephropathy who had taken 6 doses per day of preparations containing phenacetin for 20 years (range 2–15 doses for 4–45 years), Murray[46] noted that all but 2 were taking them for "psychological" reasons. He found that patients were more likely than members of the control group to report that another member of the family had abused analgesics, and suggested that "the disorder stems from abnormal attitudes to analgesics which are often family-transmitted, particularly by mothers." Patients were also

more likely to abuse alcohol, to smoke more, to abuse other drugs, and to have a history of psychiatric treatment than members of the control group.

The association between psychiatric illness and OTC analgesic abuse was also noted in psychiatric patients. Murray et al[86] reported that 42 of 181 patients admitted for psychiatric illnesses were daily "heavy" users of analgesics (less than 1 kg in the previous 6 months), and 16 were "abusers" (more than 1 kg in the previous 6 months, or more than 5 g per day). Hospital staff identified another 22 patients abusing OTC analgesics. None of the 38 abusers had chronic joint problems that would have justified the use of analgesics. Headache was the most frequent explanation, as it was in other surveys, but some patients reported using OTC analgesics to "calm me down," or "to get my strength back." Eight patients described their use as an "addiction." The psychiatric diagnoses given to the people who abused analgesics included a variety of nonpsychotic illnesses that are difficult to classify according to modern diagnostic criteria. Interestingly, although psychotic patients are very likely to abuse alcohol or other drugs,[87] none of the surveys mentions use of OTC analgesics in this group.

### *Abuse or misuse of currently available OTC analgesics?*

The high therapeutic index for currently available agents means that abuse or misuse is not as readily identified by the presence of drug toxicity as was the case with phenacetin. However, the recent surveys described above indicate that, at least in women, the drugs are frequently used to treat psychological symptoms, particularly dysphoric or depressed mood. It is also argued above that the withdrawal of phenacetin did not produce a marked change in the way in which OTC analgesics are used. Evidence of abuse or misuse of OTC analgesics, however, is much less conclusive than it is for phenacetin; this indicates a need for more data.

One problem in the recent literature is that most of the data are based on self-reported drug intake. OTC analgesics are often not mentioned when medical histories are taken,[88] and, even when specifically asked, people often under-report their use of these agents. For example, in a recent study of patients with gastrointestinal perforation, assays of platelet cyclooxygenase activity identified 13% more people who were using ASA than did a detailed clinical history.[89] This error is in the same range as that found in an Australian survey 25 years ago — urine was positive for salicylates in 10% of people who denied using OTC analgesics.[52] To the extent that people knowingly use OTC medications inappropriately, they would be expected to be more likely to deliberately hide their drug use. Thus, the levels of use reported in surveys and clinical studies probably represent the minimum levels of drug use.

As noted above, ASA, acetaminophen and ibuprophen are all on the top 10 list of drugs involved in emergency room contacts because of their use by people attempting suicide. In about half of patients with acetaminophen-induced liver failure there is evidence of suicidal intent.[32] However, there is no information on whether using an OTC analgesic to attempt suicide is associated with prior use of these agents. After excluding suicidal use, there were 2 groups of people with acetaminophen-induced liver failure, and both groups had used acetaminophen in doses exceeding 4 g per day. In the first group were people who abused alcohol and had a history of ingesting over 10 g per day of acetaminophen (i.e., more than 20 extra strength tablets). This is reminiscent of the men who abused phenacetin described in the Canadian veterans study.[37] A study of 64 patients answering "yes" to at least 1 question to the CAGE 4-question alcohol abuse questionnaire found that 20% reported daily use of acetaminophen.[90] Of the daily users, 2 used more than 4 g per day. It is likely that alcoholics use OTC analgesics to treat hangover symptoms, but it is possible that they are used for other purposes.

The second group of patients with acetaminophen-induced liver failure had been consuming lower doses — 4 to 10 g per day — and had been fasting for periods of 3 days or more, which, as with ethanol, increases the hepatotoxicity of acetaminophen.[32] One patient had taken acetaminophen to relieve a headache associated with fasting, and 9 others had had prolonged, flu-like illness. There is indirect evidence that women on diets take greater amounts of OTC analgesics. In the Canadian National Population Health Survey,[60] 77% of people who reported using diet pills also reported having used analgesic or anti-inflammatory drugs in the previous month, considerably higher than the overall figure of 61%. In addition, 76% of women with a body mass index (BMI) between 29 and 38 reported use of analgesic or anti-inflammatory

agents in the previous month. In women who had a BMI over 38 (i.e., morbidly obese individuals), the probability of use declined to 55%. To put this in perspective, with a BMI over 29 it becomes necessary to shop for clothes at speciality outlets for larger sizes, and a high proportion of these women would be expected to be trying to lose weight. The findings in the National Population Health Survey are consistent with anecdotal evidence that women who are dieting often complain about headaches.

There are a number of studies of OTC analgesic use by specific groups, including elderly people, patients who suffer from headaches and women. These focus on 2 issues.[2,91,92] The first is toxicity due to the agents themselves or due to their interactions with other drugs or substances. Elderly people are particularly at risk since they frequently take many medications at the same time; ASA, especially, interacts with many classes of drugs.[93] The second issue is the widespread belief that society is "overmedicated" and looks too readily for a pharmacological solution to problems — a statement reflecting society's negative attitude toward the use of medication. The data on use in surveys of specific groups is impressive. Chrischilles et al[94] found that 10.5% of elderly men and 14.4% of elderly women in rural Iowa were using 2 or more OTC analgesic preparations concurrently. Moreover, 75.1% of men and 66.9% of women taking analgesics reported either mild pain, or no pain at all. Combined use of prescription and nonprescription analgesics was reported by 6.4% of the men and 11.3% of the women. Variables associated with heavy analgesic use in women were poorer physical functioning and depressive symptoms. Men were more likely to use multiple products when they reported "nonspecific purposes," which the authors felt included many conditions for which analgesics are not recommended, such as stress, nerves, digestion, energy and for "things in general."

### *Headaches*

Headaches are covered separately because they are the most common reason to use OTC analgesics, and it is estimated that headache sufferers in Canada use them an *average* of 3 times a week.[2] In other words, people who suffer from headaches use OTC analgesics regularly at relatively high levels. Moreover, it has been proposed that the abuse of OTC analgesics plays a causal role in the development of chronic daily headaches (defined as a headache more than 20 days per month).[95] The evidence supporting this notion is weak, but because of the ubiquity of OTC analgesic use by people with headaches it is a very widely held belief. The discussion below raises more questions than it answers, and indicates that it is necessary to obtain detailed drug histories from patients who suffer from headaches.

The idea that analgesic abuse is a causative factor in the development of chronic daily headaches originated in a study purporting to show that amytriptyline was more efficacious if other miscellaneous analgesic agents were withdrawn.[96] Unfortunately, this difference is not evident when the whole sample, including those who dropped out, is considered. The dropout rate for people denied analgesics was 54%, whereas it was only 7% for those who were allowed to take analgesics. Yet the notion that analgesics produce a "disregulation of nociceptive systems"[97] has persisted, probably fuelled by Calvinist social attitudes that attribute ill health to unhealthy lifestyle, poor self-control and so on.[98]

The data on the role of analgesic abuse by those who suffer from headaches are clouded by the fact that many studies do not separate OTC and prescription drugs. Ergotamine and related drugs can undoubtedly produce tolerance, dose escalation and severe headaches on withdrawal.[95,99] Caffeine, another common constituent of both prescription and OTC headache remedies, also produces headaches on withdrawal.[100,101] The observation that people who suffer from headaches tend to prefer analgesics that contain caffeine,[81] together with the higher coffee consumption by those who use analgesics,[57] support the notion that caffeine withdrawal is a significant factor in the overuse of analgesics. However, it is also possible that headaches are the primary reason that both OTC analgesics and caffeine are used. Caffeine-withdrawal headaches are not severe and dissipate with less than a week of abstinence, so termination of caffeine intake should solve the problem quickly. Many prescription headache medications also contain opioids and barbiturates, both of which can lead to the development of tolerance, physical dependence and an abstinence syndrome on withdrawal, but the withdrawal syndromes do not feature headaches as a major symptom.[102] Barbiturates could, however, produce hangover headaches.

Chronic analgesic-induced headaches are also associated with the use of OTC analgesics containing only

acetaminophen or ASA,[95] for which there is very little evidence of tolerance or physical dependence.[14,103] The obvious explanation for the correlation between chronic headaches and analgesic use — that people with more pain take more drugs — seems not to have received serious attention. In addition, there is some evidence that high doses of phenacetin produce acute headaches as a side effect.[104,105] It is possible that currently available OTC analgesics cause headaches in susceptible people, although one would expect to observe headaches in those who take NSAIDs for inflammatory conditions if this were the case.

*Summary*

Despite the anecdotal nature of most of the evidence, there is no doubt that phenacetin was abused. Patients continued to use the drug despite knowledge that it was producing serious kidney damage; they engaged in drug-seeking behaviour suggestive of dependence; there was an association with the abuse of other psychoactive agents; and phenacetin was used to alleviate psychological symptoms. There is also evidence suggesting that the drug was used to produce intoxication, which is discussed below. As far as currently available OTC analgesics are concerned, they are widely used to treat symptoms for which they are not recommended, and some of the people who use them to treat mood states, anxiety, sleep problems and stress may be in need of treatment with more specific and efficacious agents. The extent to which OTC analgesics are taken regularly for undefined purposes is not known. A small number of people experience very serious toxic effects after using higher doses than recommended. It is not known how many people use high doses and do not suffer toxic effects, or if overuse of OTC analgesics contributes to morbidity and mortality from other causes. As far as analgesic-induced headaches are concerned, the data are equivocal and do not support withdrawal of analgesics in patients with headaches, although many patients who suffer from headaches probably need to rationalize their drug use. In fact, the literature dealing with abuse or overuse of OTC analgesics, either for pain or other problems, rarely mentions or suggests alternative treatments. Rather, the focus is on simply getting patients off the drugs they are taking. Whether the drugs produce psychological effects that could be considered in the context of addiction is discussed below.

## Are adjuvant drugs in analgesic mixtures addictive?

Although heavy use of preparations containing a single ingredient does occur,[106] regular users and abusers of OTC analgesics are more likely to use a preparation containing ASA or acetaminophen (or phenacetin/ASA in the past) along with other active agents.[11,37,45,46,54,107] The association between the abuse and use of mixtures has led to the suggestion that the adjunctive agents, primarily caffeine and codeine, produce psychotropic effects that lead to dependence.[47] Several questions arise from the tendency for people who abuse analgesics to prefer combination mixtures. Some of these relate to the pharmacological actions of the adjuvant agents, and others relate to the possible differences between single agents and the kinetics of mixtures.

*Mixtures containing caffeine*

The simple explanation for the preference for analgesics that contain caffeine is that they are more effective because caffeine potentiates the analgesic actions of a wide variety of analgesic agents.[15] (Caffeine alone has minimal effects on pain thresholds.[40]) This is consistent with the fact that coffee consumption was positively associated with OTC analgesic use in the Norwegian survey.[57] Recently, a large study comparing the treatment of tension headaches with acetaminophen, acetaminophen plus caffeine, and ASA found, as expected, a significant potentiation of the analgesic effects by caffeine.[108] The regular caffeine intake of the subjects (varying from 0 to over 500 mg per day) was not related to whether the potentiating effect occurred, implying that tolerance to, or dependence on, caffeine is not related to its actions as an analgesic adjuvant. In addition, there were significantly more side effects (stomach discomfort, nervousness and dizziness) with the preparations that contained caffeine. This suggests the possibility of a pharmacological interaction, since neither acetaminophen nor caffeine would be expected to produce such side effects by themselves at the doses used.

*Mixtures containing codeine*

There has been extensive speculation that overuse of OTC analgesic mixtures containing 8 mg of codeine reflects opioid abuse and possibly dependence. Direct

evidence for this is lacking, and case reports that imply support for the notion in their abstracts are often misleading: for example, a 54-year-old man forged prescriptions for Tylenol No. 4 (60 mg codeine per tablet) to treat headaches over a 10-year period.[109] If overall rates of opioid dependence were higher in countries that allow codeine in OTC preparations, this would provide indirect support for the notion that use of OTC codeine was one route to development of opioid dependence. However, figures for rates of opioid dependence in countries with and without OTC codeine, both from the 1960s[110] and more recently,[111] do not support this. The historical data on consumption of oral opioids from the 19th century also fail to support the notion that OTC availability of oral opioids, even in unrestricted quantities, leads to a high rate of severe opioid dependence. From pharmacy records, Courtwright[112] estimated that the prevalence of persistent, regular use of high doses of oral preparations containing opiates in the United States was only about 4 people in 1000 in the last quarter of the 19th century. Interestingly, like people who abuse analgesics today, the persistent users were primarily middle-aged women, although there were some Civil War veterans who used injectable morphine. One would also predict that people who become opioid-dependent through the use of OTC codeine would be more likely to use prescription drugs than heroin available on the street. Data on this are not readily available, but there is no reason to believe that double-doctoring and faking of pain complaints to obtain opioids is more common in Canada (where codeine is available OTC) than it is in the United States. To the extent that this does occur, anecdotal accounts suggest that it is more common when supplies of preferred illegal drugs are short.[113,114]

An alternative hypothesis is that the combination of a low dose of an opioid with an NSAID increases the addictive properties of the mixture, even though the amount of codeine is insufficient to promote opioid dependence. If this is the case, then people who abuse analgesics should clearly prefer mixtures containing opioids and countries that allow small amounts of codeine in OTC preparations should have higher levels of OTC analgesic abuse. Anecdotal evidence indicates that medical personnel who practised during and after the epidemic of analgesic nephropathy are convinced that it was the codeine that led to overuse. Furthermore, the 2 Canadian studies of analgesic nephropathy indicate that the majority were using APC-C (ASA, phenacetin, caffeine and codeine).[45,49] However, the preparations used most frequently by patients with analgesic nephropathy in various regions of the UK varied considerably, with the common factor being caffeine and phenacetin rather than codeine.[48] Data show that the United States, where OTC preparations do not contain codeine, had higher levels of intake of OTC analgesics than the other 8 countries surveyed at that time.[78] More recent data for elderly people indicate, if anything, higher rates of usage in the United States than in Canada.[94,115]

### *Kinetic properties of proprietary mixtures*

Alterations in the kinetics of any of the constituents of the mixture, rather than the pharmacological actions of caffeine or codeine, may promote the preference for combination analgesics. This argument is based on 3 sets of facts. First, it is well known that the degree of abuse of a wide variety of psychotropic drugs is related to the kinetic properties of the preparation available or the route of administration used. For example, opiates are more likely to be abused when a method of administration is available that allows rapid uptake and penetration into the brain. Thus, the availability of oral tonics containing opium led to widespread oral use in the 19th century, with little social perception that a problem existed despite their high intake by a small proportion of the population. However, the intoxicating and addictive nature of smoked opium, in which absorption is more rapid, was obvious, and the first controls on opium products related specifically to smoking opium. The development of injectable morphine and heroin produced even more serious abuse patterns.[112] The pharmacokinetic rule is that more rapid absorption leads to a higher and earlier peak drug level. For psychotropic drugs, the effects are much more salient when high brain levels are reached rapidly.

Second, the absorption of drugs in mixtures may be altered both by the active and the inactive ingredients in the mixture. Caffeine is relatively insoluble in aqueous solutions, and solubility is improved by the addition of citric acid, sodium salicylate, or sodium benzoate.[116] We could not find any data on whether ASA, acetaminophen or phenacetin alter absorption of caffeine or vice versa, but such effects are not impossible. If this is the case, there may be a higher, and earlier, peak effect for the agents in an analgesic mixture than for any

of the agents alone; this could explain the "dizziness" produced by acetaminophen and caffeine.[108]

Third, the absorption of all oral preparations is strongly influenced by nonpharmacological factors. Phenacetin, ASA and acetaminophen are nearly insoluble in aqueous solutions, and effervescent formulations of acetaminophen or ASA are absorbed twice as fast as tablets.[117,118] Particle size is also very important in both the rate and completeness of absorption by the gastrointestinal tract; an emulsifying agent to prevent hydrophobic particles from clumping further increases the rate of absorption.[105,119] The magnitude of the potential differences is illustrated in Fig. 5, which shows plasma salicylate levels for a proprietary preparation containing ascorbic acid and ASA.[120] Even in the case of "plain" ASA, the dissolution rates of 5 brands were highly variable.[121,122] In addition, there are individual differences in absorption rates that relate to gastric motility, pH and, of course, the presence or absence of food.[14,123] Once absorbed into the bloodstream, all of these agents pass freely through the blood-brain barrier, so that higher plasma peaks reflect higher CNS levels. These data indicate that there may be very large differences between proprietary preparations in the rate of absorption, the peak level reached, and hence, the potential for CNS effects: advertisements for "fast pain relief" may, in some cases, actually be supported by data.

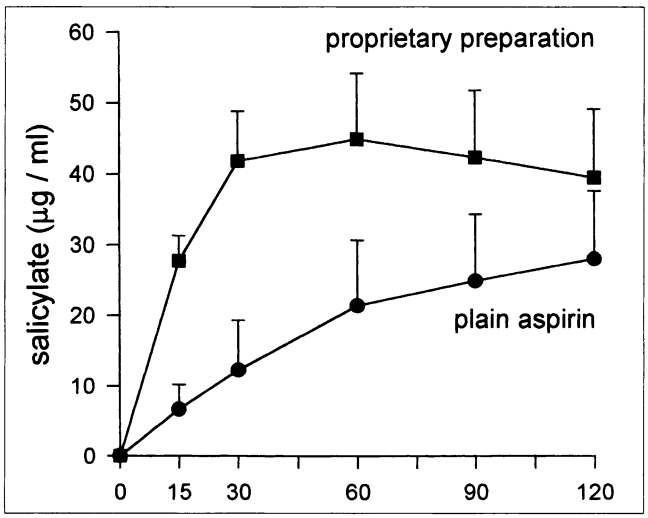


**Fig. 5: Plasma salicylate levels for plain ASA (aspirin) and a proprietary formulation incorporating 400 mg of ascorbic acid. The implication is that some advertisements for "fast pain relief" may in fact be true. The slow rise in plasma levels for plain ASA would be very unlikely to produce detectable psychotropic effects if ASA had such action. Data from Staudacher and Muller.[119]**

*Summary*

Proprietary mixtures may be more likely to produce psychotropic effects as a consequence of altered kinetics of any of the constituents, and the differences in physiochemical properties between proprietary formulations can lead to large differences in the pharmacological activity of different preparations of the same basic pharmacological agent. Of course, whether these factors are relevant to analgesic abuse is predicated on whether there are any psychotropic effects produced by OTC analgesics.

## Psychotropic effects of OTC analgesics

*Phenacetin*

Eade and Lasagna[124] compared the effects of phenacetin, ASA and acetaminophen to those of those of pentobarbital and amphetamine. The effects of acetaminophen and ASA were not significantly different from those of a placebo, but phenacetin was classified as "unpleasant," and as similar to pentobarbital. Since both of these agents are often abused, it is expected that they would have been classified as "pleasant." However, it should be pointed out that former opiate addicts[125] and normal volunteers[126] often consider morphine unpleasant, and the subjective effects in experimental situations cannot be used to determine the likelihood that a drug will be abused — the important point is that there were subjective effects. Prescott and Cantab[119] unexpectedly found that phenacetin had psychological effects while they were investigating absorption rates for different sizes of particles. Whereas Eade and Lasagna found that phenacetin depressed mood, energy and mentation, Prescott and Cantab found that it caused lightheadness associated with a sense of unreality that was considered pleasant. Subjects also felt "unsteady and weak at the knees, and their ability to concentrate was compromised." These effects were more prominent and more frequent for finely ground phenacetin mixed with an emulsifying agent, which produced the highest and most rapid increase in plasma phenacetin levels. The descriptions of psychotropic effects of phenacetin are consistent with anecdotal reports, mostly from Germany, going back to the 1890s (cited in Eade and Lasagna[124]).

Whereas acute high phenacetin doses are intoxicating, lower doses taken chronically produce more subtle, but still desirable, psychotropic effects. Krumholz et al[127] administered ASA, APC (ASA, phenacetin and caffeine), mephenoxalone, and a placebo to hospital personnel for 3 weeks. The APC mixture significantly improved mood scores; ASA alone was less effective.

*Currently available preparations*

The studies described above indicate that phenacetin has psychotropic actions that suggest an intoxicating effect at high doses, and mild mood-elevating effects at lower doses. These properties appear to be similar to the characteristics of CNS depressants such as alcohol and barbiturates. However, if the primary cause of analgesic abuse was phenacetin, and preparation preference was based on physiochemical properties promoting rapid absorption, then use of OTC analgesics should have decreased when phenacetin was taken off the market. As Fig. 6 indicates, this was not the case — instead, there was a widespread switch to preparations that contained acetaminophen and ASA, and acetaminophen and ASA use increased more in countries that had high phenacetin use than those with lower levels of use.

The data on psychotropic effects of currently available OTC analgesics are limited. There are case reports of the use of ASA to produce intoxication (e.g., Savage[106]), but these most likely reflect salicylate poisoning.

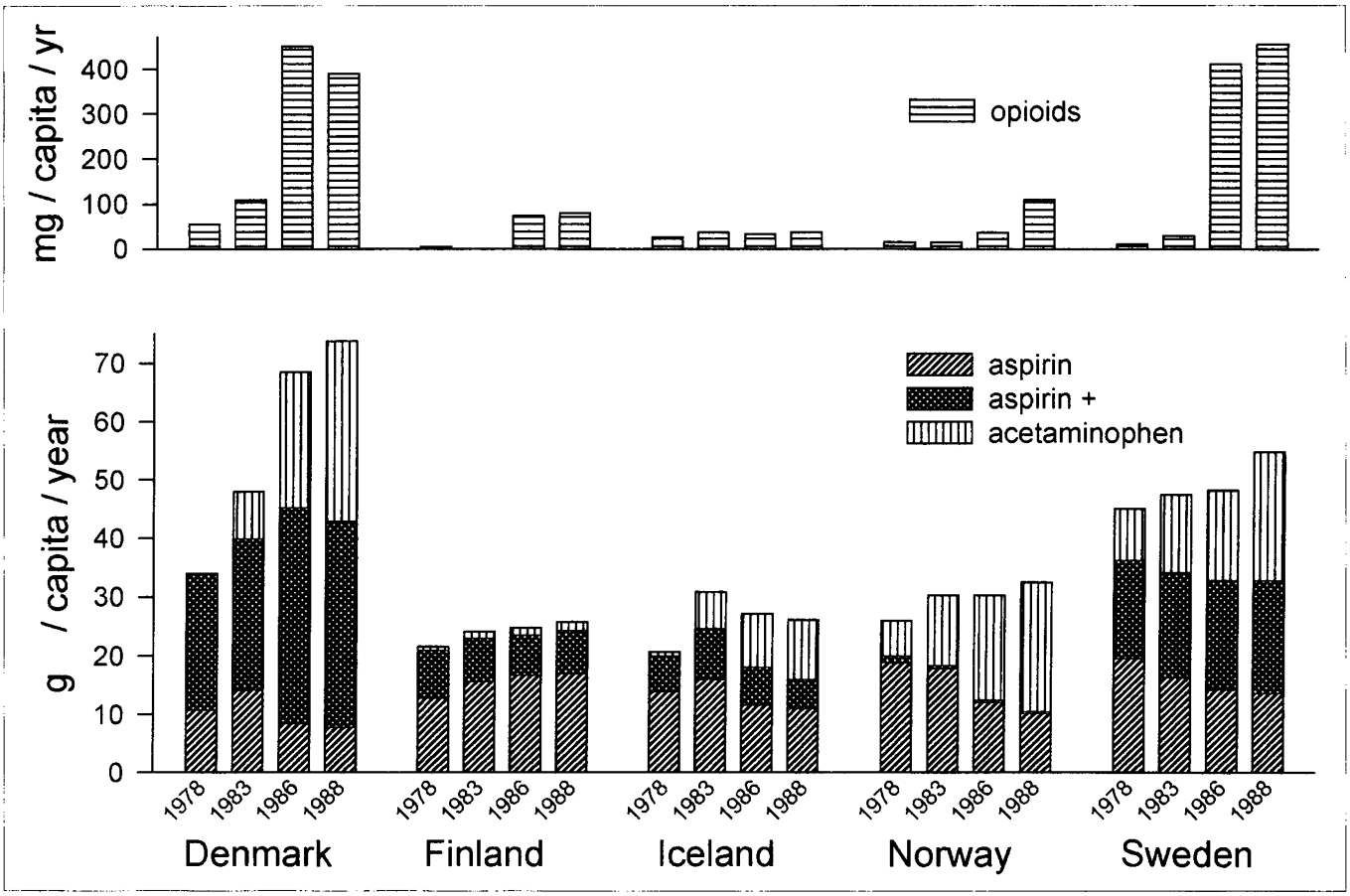


**Fig. 6: Bottom: Consumption of ASA (aspirin), ASA in combination with another agent (aspirin+) and acetaminophen in 5 northern European countries between 1978 and 1988. Use at the beginning of the period did not differ much from use when phenacetin was available. In all countries, intake increased during the decade; in Denmark and Sweden the increase was dramatic. Top: Consumption of opioids, expressed as morphine equivalents, during the same period. The increase in opioid use in some countries in the late 1980s coincided with concern about treating pain in patients with terminal cancer. Given that some of the morphine used would have been converted to codeine (with a 10-fold loss in potency), the opioid use shown was low, even in Denmark and Sweden. Data from Ahonen et al.[10]**

Wolff et al[40] found that ASA had a mild sedative effect that did not increase as dose increased, and there was no sense of contentment, euphoria or apathy. However, repeated, larger, nontoxic doses produced slight difficulties in attention and concentration. ASA also antagonized the sedative effects of ethanol in studies of animals, so that mice or rats awoke with higher blood-alcohol levels.[128,129] This raises the question of whether alcoholics might use OTC analgesics to counteract some of the effects of alcohol. Recent studies of the effects of ASA and acetaminophen have focused on sleep (and the relation between sleep and temperature regulation). Both drugs disrupt sleep, increase waking time and decrease slow-wave sleep in normal people,[130,131] and they antagonize the Δ sleep-enhancing properties of hyperthermia.[132] However, in the presence of morbidity from various causes, acetaminophen improves sleep even in the absence of pain.[133–135] In a study comparing side effects of acetaminophen and ibuprofen, 2.1% and 0.8% of patients, respectively, reported CNS side effects such as dizziness and drowsiness,[136] although the difference is not statistically significant. There is, therefore, evidence that the use of OTC analgesics for sleep problems has a pharmacological basis.

Chronic intake of some of these agents may lead to altered kinetics. This appears to have been the case for phenacetin in a study of the effects of chronic administration on the lethal dose in rats.[103] Treatment for 1 week increased the lethal dose by a factor of more than 2, likely due to the increasingly rapid conversion of phenacetin to acetaminophen, which is less toxic. Prescott et al[105] found that phenacetin reached peak plasma levels at 30 minutes, whereas acetaminophen levels continued to rise slowly for 60–90 minutes, but this may not reflect the kinetics in heavy users. In people with high intakes of analgesics, acetaminophen levels may rise quickly enough to contribute to the psychological effects in people who abuse phenacetin. It is also possible that the negative findings concerning the psychotropic effects of ASA and acetaminophen in the study by Eade and Lasagna[124] were due to the fact that the preparations they were using were absorbed more slowly than the proprietary formulations preferred by heavy users of OTC analgesics.

*Animal studies*

There have been few attempts to examine self-administration of NSAIDs in animals. Hoffmeister and Wuttke[137] examined intravenous self-administration of ASA and combinations of ASA with codeine and caffeine in monkeys. When given 24-hour access to 2.4 mg/kg per injection of ASA for 2 weeks, bar pressing increased above operant rates. The daily intake reached a plateau at 100 mg/kg per day, the equivalent of 5 doses per day at the recommended dose to treat acute pain in primates, 20 mg/kg — in other words, a pharmacologically active amount. Substitution of a higher dose of ASA, 10 mg/kg per injection, completely suppressed bar pressing. There was no evidence that ASA would substitute for codeine in animals trained to self-administer the codeine, indicating that ASA did not alleviate a mild opioid withdrawal syndrome. Combining ASA with codeine produced a dose-dependent *decrease* in self-administration rates, which could indicate that the combination was aversive. Alternatively, the decrease may reflect increased reinforcing potency, such that the combination was equivalent to a higher dose of codeine per injection, which would also decrease response rates. The effect of caffeine, either alone or in combination with codeine or ASA, was weak. The data suggest a weak reinforcing effect of the low dose of ASA.

An interesting study in rats indicated that normal animals would not drink a solution of suprofen. However, when arthritis was induced by injecting Freund's adjuvant, rats drank a pharmacologically active amount. Colpaert et al[138] interpreted this as evidence that the rats were self-medicating for pain. However, it is also possible that rats were treating the malaise (indicated by hunched posture, ptosis, piloerection, and reduction of activity) and sleep disturbance that accompanies generalized illness — in other words, using the medication to "feel better."

Whether OTC analgesics produce tolerance or physical dependence that contributes to dose escalation is not clear. In treatment of rheumatic diseases, tolerance to the therapeutic effects of NSAIDs does not seem to occur.[14] As noted above, rats became tolerant to the lethal effects of phenacetin, but this was probably due to more rapid degradation of phenacetin to acetaminophen. The regulation of COX and prostaglandin (PG) receptors is currently an active area of investigation. In newborn pigs, 48 hours of treatment with indomethacin is sufficient to up-regulate $PGE_2$ and $PGF_{2\alpha}$ receptors on cerebral microvasculature.[139] In vitro studies of the mechanisms of action of NSAIDs indicate that they reduce COX 2 expression to varying de-

grees over a 4-hour period.[140] We were unable to find studies involving longer-term application of NSAIDs.

*Summary*

Phenacetin produces intoxication that generally resembles that produced by low doses of CNS depressants. The effects of acetaminophen, ASA, and of proprietary mixtures of these agents with codeine or caffeine on psychological functioning have never been adequately examined, but there is a small amount of supportive data. In view of the variations in bioavailability of different formulations of these agents, it will be necessary to verify that the drugs are adequately absorbed. It may be possible to predict which brands are rapidly absorbed by obtaining data on preferences from people who use high doses of OTC analgesics.

## Conclusions

The available information suggests that abuse and misuse of OTC analgesics may be associated with 2 different groups of problem users. The first are those with chronic pain. The morbidity in this group might be reduced by using treatments that are specifically effective for chronic pain, such as low doses of some antidepressant agents.[73] Other patients with chronic pain might be better off on opioids under medical supervision,[141] since opioids are less toxic for long-term use than OTC analgesics, the most serious side effect being constipation.[142] The second group seems to be using OTC analgesics to treat dysphoric mood states, sleep disturbances and so on. Some of these people may be turning up in the Drug Abuse Warning Network statistics for emergency room contacts involving suicide attempts, since at least some of them may be clinically depressed and would have the drugs on hand if they wanted to attempt suicide. This group might benefit from specific therapy for mood disorders or from sleep management programs. Whether OTC analgesics have direct mood effects in people without pre-existing pain or dysphoric mood needs further investigation. Certainly, all medical histories should contain information about the use of OTC analgesics, keeping in mind that people who are misusing them are likely to deny or under-report their use.

Currently there is considerable pressure from private and public insurers to make more pharmaceuticals available over the counter, which would shift costs to the consumer. The pharmaceutical industry supports this because it would allow advertising directed at the consumer, which would increase sales. Despite these trends, problems are foreseen if more products become available over the counter. Some of these concerns are valid. The potential for drug interactions increases if patients are taking OTC drugs that physicians do not know about.[143,144] Package inserts are written at a grade 10 reading level, although a large proportion of consumers function at a grade 5–7 level, and the print on many package inserts is so small that many elderly consumers cannot read them without special aids.[145] There is also a concern that the availability of OTC medications may lead people to postpone seeking medical help for serious conditions, and that making more drugs available over the counter and having physicians recommend them "encourages patients to think that there is a drug treatment for every ailment."[146] The trend to increase the range of OTC medications available requires a concurrent public health effort to encourage rational self-medication. This effort needs to be based on information about the way OTC drugs are used, and in what circumstances they are used. In the case of analgesics, the largest group of OTC drugs in terms of sales, there is an urgent need for more information on the way these agents are being used.

## Acknowledgement

This work was supported by the Natural Science and Engineering Research Council of Canada and the G.W. Stairs Fund.

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