GP Handbook

Pharmacology

(last update 20090705)

ANTIBIOTICS IN RESPIRATORY INFECTIONS

Acute Otitis Media

Use of antibiotics can be deferred for 48 hours since 1/3 of all otitis media are viral and therefore self-limiting. Our recommendation is to prescribe a short course of antibiotics for children who are at risk for complications (eg when the child is in obvious, severe pain and the eardrum is red and bulging). Empirical coverage for *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella* species is recommended.

For children who need antibiotics, amoxycillin (Ospamox, 80mg/kg/d) or amoxycillin-clavulanate (Augmentin) is recommended. Clarithromycin (Klacid), azithromycin (Zithromax) are useful for patients allergic to penicillin.

Oral antibiotics can often be given for 5-7 days in children over 6 years old. A full 10-day course, however, may be indicated for younger children and for those with complications. Avoid local treatment with antimicrobial eardrops (*Lisby-Sutch et al., 1990; "Clinical uncertainty clouds pharmacoeconomic assessment of otitis media therapy," 1995*).

Acute Rhinosinusitis

Green or yellow nasal discharge is not specific to bacterial infections and is NOT an indication for antibiotic treatment. Antibiotic treatment (eg Augmentin or Klacid) should be deferred unless there are severe symptoms, such as fever greater than 39 ºC, maxillary pain and/or swelling, or cough with purulent rhinorrhea for more than 7-10 days. Local symptoms can be treated with intranasal decongestants together with oral antihistamines especially if allergic rhinitis is a possibility.

Common Cold

Antibiotics should not be given for common cold even in the presence of mucopurulent rhinitis.

Acute Bronchitis

Most cases are self-limiting, and viral in aetiology. Antibiotics should only be used in the elderly, patients with signs and symptoms of pneumonia. Routine chest x-ray should be performed in patients with acute cough illness lasting > 2 weeks, especially in poor risk patients, to rule out pneumonia, pneumonitis, cancer and TB.

Exacerbation of COAD

Patients with acute exacerbation without increase in purulent sputum do not need antibiotics unless there is clinical or radiological (eg consolidation on a CXR) evidence of pneumonia. The antibiotics of choice are Augmentin, Klacid, Zithromax and Zinnat (cefuroxime).

Acute Laryngitis

Antibiotic treatment should be reserved for high-risk patients, patients with severe symptoms, or in the presence of an identifiable organism on Gram stain or culture.

If symptoms persist > 3 weeks, the condition is classified as chronic laryngitis, for which an underlying cause (eg polyps, cancer, TB and GERD) must be further investigated.

Sore Throat

Antibiotics are widely used (or abused) for treatment of sore throat, although very few cases are bacterial in aetiology. Inflammed pharynges or enlarged or even exudative tonsils do not necessarily indicate a bacterial cause.

Two systematic reviews on a total of 19 trials failed to show any beneficial effect from antibiotics for the cure or symptomatic relief of the common cold, but the treatment groups reported more side effects. A local study by Dr K Choi confirmed the following points:

- Bacterial infection accounts for only 15% of all sore throats.
- The commonest bacteria isolated are Group A and Group G streptococcus.
- Penicillin V for 10 days remains the treatment of choice because of its proven efficacy, narrow-spectrum, safety and low cost.
- Erythromycin and tetracycline should not be used because of their high resistance rate.

Antibiotics should not be used with the specific intention to prevent development of rheumatic fever or acute glomerulonephritis. Antibiotics may reduce the risk of cross-infection in closed institutions but should not be used routinely for this purpose in the general community.

One important but often overlooked fact is that, even if the patient does indeed suffer from a bacterial infection, antibiotics may still not be needed. Rest, good hydration and symptomatic treatment may be all that is necessary for a complete and uneventful recovery.

Modified Centor Criteria

For diagnosis of streptococcal tonsillopharyngitis, a scoring system may be employed as follows:

One point is awarded for each of:

- ***Fever (> 38°C)***
- ***Absence of cough***
- ***Swollen, tender anterior cervical nodes***
- ***Tonsillar swelling or exudates***
- ***Age 3-14***

One point is deducted if:

- ***Age > 45***

According to the scoring system,

- 1 point or less: no further testing or antibiotics
- 2-3 points: throat swab culture - antibiotics only for positive cultures
- 4-5 points: empirical antibiotics +/- throat swab

Even at points 4-5, the risk of bacterial (streptococcal) infection is only 51-53%.

Throat swab

In addition to traditional culture, rapid antigen detection tests (RADTs) are commercially available

for identifying group A beta-haemolytic streptococci directly from throat swab. They have the advantage over culture of producing results much faster. The results are highly specific for group A streptococci. Unfortunately the sensitivity of most RADTs ranges between 80% and 90%.

In daily practice however, getting throat swabs from patients is much easier said than done, considering the inevitable inconvenience and cost. Without objective microbiological data, most experienced physicians would recommend the following:

- 2-3 points: observation – antibiotics only if the patient deteriorates in 48 hours
- 4-5 points: empirical antibiotics – clinical review in 48 hours

Symptomatic treatment:
Paracetamol is effective in relieving the symptoms of fever, and sore throat in both adults and children. NSAIDs are not much more effective but cause more side effects. Aspirin is contraindicated in children under the age of 12 because of the risk of Reye's syndrome. The following may provide extra symptomatic relief:

- Lozenges: Pharynx, Dequadinium
- Gargle: Thymol gargle, Benzydamine (Difflam)
- Anti-inflammatory enzymes: Lysozyme, Papain, Flemyzme

Steroids
If symptoms are severe a short course of oral steroid (eg prednisolone 40-60mg/day x 3/7) may be considered. A Mayo Clinic study in 2003 found that a single 10 mg dose of dexamethasone provided safe, effective and inexpensive treatment for bacterial or viral pharyngitis (sore throat). Explain carefully to the patient that while steroid may offer excellent symptomatic relief, it does not treat the underlying cause of sore throat. Steroid therapy is contraindicated in hepatitis B carriers.

CHEMOTHERAPY OF TUBERCULOSIS

Summary

A 6-month standard combination regimen with 4 drugs in the initial phase is recommended for uncomplicated new cases of pulmonary tuberculosis (TB), while a 9-month standard regimen starting with 5 drugs is recommended for retreatment cases.

Multidrug-resistant TB requires individually tailored treatment regimens as guided by drug susceptibility testing. Recommendations for extrapulmonary TB are based on relatively limited data. A longer duration of treatment is generally required for patients with DM, silicosis and compromised immunity. During pregnancy, streptomycin should be avoided and the safety of most second-line agents has not yet been ascertained.

Potentially hepatotoxic agents should be used with caution in patients with liver dysfunction. The renal route of elimination of streptomycin, ethambutol and some second-line agents necessitates caution and dosage reduction in case of renal impairment.

Uncomplicated Pulmonary TB

New case*: 2HRZ+(E or S) / 4HR

FOUR drugs — isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin — are recommended for the initial 2-month phase of treatment, as the rate of initial resistance to isoniazid is more than 4% in Hong Kong. TWO drugs — isoniazid and rifampicin — are recommended for the 4-month continuation phase, ie the total treatment duration is 6 months.

The drugs may be given on a daily or thrice-weekly basis in both the initial and the continuation phase. Studies have shown that daily administration for 2 months followed by thrice-weekly treatment for 4 months can be equally efficacious. For patients with extensive disease, the 2-month initial phase may be extended to 3 or 4 months, depending on clinical, bacteriological, and radiological responses, while the total duration of treatment may still remain at 6 months. An occasional patient may need prolongation of therapy to beyond 6 months. If there is a suspicion of drug-resistant TB (eg in contacts of patients with drug-resistant TB), the initial phase of treatment may be similarly extended, pending the conventional drug susceptibility test results.

**Drugs: E, ethambutol; H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide*
**Duration: this is shown by the figures (in months) in front of the drug combinations; the slash "/" is used to separate different phases of treatment*
**Frequency: this is shown by the subscripts attached to the individual drugs (ie subscript "3" indicates thrice weekly administration) and absence of subscript indicates daily administration*

Retreatment case*: 3(4)HRZES / 6(5)HR±E

FIVE drugs — isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin — are recommended for the initial 3-4 months, depending on the timing of the availability of sensitivity test results, the rate of smear conversion, extent of disease, and probability of drug resistance.

Isoniazid and rifampicin (also with ethambutol if the disease is extensive or the sensitivity test pattern is unknown) are recommended for the continuation phase, ie the total treatment duration is 9 months. If the sensitivity test results that are available subsequently are unfavourable, the above regimen may

need to be modified.

Drug-Resistant TB

Refer.

Extrapulmonary TB

TB of bones and joints
2HRZ + (E or S) / 10HR

TB lymphadenitis

- For peripheral disease which commonly involves the cervical region and where there are only solitary/few affected lymph nodes together with normal chest X-ray, the treatment is the same as that for new case of uncomplicated pulmonary TB: **2HRZ+(E or S) / 4HR**.
- For more centralized disease /multiple / larger lymph nodes the same treatment should be extended to 9 months, ie **2HRZ+(E or S) / 7HR**.

The clinical response of TB lymph nodes during treatment may be quite unpredictable, sometimes with paradoxical increases in size probably due to immunological reactions. Residual nodes may still be palpable after completing the full course of treatment

Other Clinical Situations

DM
2HRZ+(E or S) / 7HR

Pregnancy
Basically, rifampicin, isoniazid, ethambutol, and pyrazinamide can still be used, although the manufacturers of rifampicin advise caution during pregnancy. Pyridoxine is sometimes recommended for pregnant women receiving isoniazid. Streptomycin should be avoided because of ototoxicity to the foetus. The safety profiles of the second-line drugs and ofloxacin have not been ascertained and thus these drugs should also be avoided. The taking of anti-TB drugs is by itself not an absolute contra-indication to breast feeding.

Children
The treatment regimens are essentially similar to those for adults, except that ethambutol should be avoided in children until they are at least 6 years old and capable of reporting symptomatic visual changes accurately. The drug dosages need to be calculated according to the body weight and may have to be adjusted, especially during the period of adolescent growth spurt.

Geriatric patients
Basically, the treatment does not markedly differ from that in the younger population. However, due regard must be paid to the physiological, psychological and social changes as well as the increased prevalence of co-morbidity that may be associated with aging. As the risk of hepatotoxicity is higher especially in those with malnourishment, some individual tailoring of dosage, say by using isoniazid 200 mg instead of 300 mg once daily and pyrazinamide 1 gm instead of 1.5 gm once daily may be warranted. Pyridoxine supplement should also be considered for those with poor nutrition or at increased risk of neuropathy. When the drug susceptibility pattern of the cultured bacilli is known to be favourable, use of rifampicin and isoniazid together may prove sufficient for diseases with limited bacillary load. A total duration of 9 months is required for co-administration of these 2 drugs. Use of ethambutol can be problematic in many old patients with poor baseline

visual function or difficulty in assessing visual acuity.

Liver Dysfunction

Transient changes in bilirubin and SGPT levels are relatively common during anti-TB chemotherapy and do not signify true hepatotoxicity.

Drug-induced hepatitis which occurs more commonly in patients with compromised liver reserve such as in chronic hepatitis B and C infection and alcoholic liver disease necessitates cessation of therapy. In these patients with pre-existing liver diseases, routine monitoring of LFT is required during anti-TB treatment. When the TB disease is mild or has improved markedly, one can wait until the LFT becomes normal before gradually re-instituting the conventional anti-TB drugs. Whenever possible, isoniazid and rifampicin should be included so that treatment duration will not be unduly prolonged. In face of extensive disease when delay in therapy is not acceptable, ofloxacin 400-600 mg qd can be used together with streptomycin and ethambutol as an interim regimen.

Renal Impairment

The development of drug-induced renal impairment is an indication for withdrawal of the drug such as streptomycin or rifampicin. If there is pre-existing renal impairment, rifampicin, isoniazid, and pyrazinamide can be given in the normal dosages. However, in severe renal failure, it is recommended that isoniazid should be given at 200 mg once daily with pyridoxine to avoid peripheral neuropathy.

Streptomycin and ethambutol are the two main drugs that are dependent on the renal route for Clearance, and appropriate dosage reduction should be made. Regular monitoring of RFT is mandatory if these drugs are to be used for patients with renal impairment.

DOSE FREQUENCY

Smart Dosing

A lot of patients experience different severities of the same symptoms during different times of the day. A common example is a patient with hyper-responsive airways syndrome who coughs moderately during daytime, but severely at night. Prescribing a medication in uniform dosage to relieve symptoms in this situation may prove ineffective. A better way to relieve symptoms while minimizing side effects is to prescribe a lower dosage of cough suppressant for daytime relief, and a much higher dosage to cover night-time symptoms, eg Codaewon ½ tab qid + Codipront 1 cap hs. Please note that with this prescription the patient will take half a tablet of Codaewon AND one capsule of Codipront before they retire.

The QID Dosing

What do "qid" really mean? In TYMP "qid" means 4 times a day – breakfast, lunch, dinner and bedtime. So it really means "tds + hs". "bd" means 2 times a day – breakfast and dinner. As you can see "bd" is different from "om + hs".

The PRN Dosing

Some medications can only be prescribed meaningfully on a strictly "prn" basis. Examples include lozenges, TNG, and artificial tears. The prescription should look like this:

- Pharynx loz tab 1 prn for 12's
- TNG tab SL prn for 10's

"Pharynx tab 1 qid prn" means the patient is advised to take one lozenge not more frequently than 4 times a day, even if their throat is burning! Is this what we want? Speaking of "prn", if we prescribe Dhamol 500mg qid prn for fever for 3 days, we are telling our patient that we expect them to have fever for 3 days, and that they should treat their own fever on an "as required" basis for 3 days! Is this what we want? My advice is that we should just give "prn" medications sparingly so as not to induce misunderstanding. A well-known example is Dhamotil. Tab 2 qid prn for 6 doses is usually sufficient for all but the most severe diarrhoea.

DRUG ABUSE

Definitions

Drug abuse refers to taking drugs without following medical advice or prescription, or the indiscreet use of dangerous drugs for non-treatment purposes.

Dangerous Drugs ("DD") is understood as a legal term representing those medicines which are legally classified as such by the Dangerous Drugs Ordinance (Cap. 134) in Hong Kong.

Drugs Commonly Abused in Hong Kong

(1) Opiates/opioids: eg heroin, opium, morphine, codeine, methadone, meperidine / pethidine, fentanyl, hydromorphone, oxycodone
(2) Hallucinogens: eg LSD, magic mushroom, PCP
(3) Cannabinoids
(4) Stimulants: eg amphetamine, cocaine
(5) Sedatives-hypnotics: eg benzodiazepines, barbiturates, methaqualone, zopiclone and zolpidem
(6) Volatile solvents: eg glue, thinner
(7) Over-the-counter (OTC) medications: eg cough mixture, cough tablet, antihistamine
(8) Others: eg 3,4-methylenedioxymethamphetamine (MDMA), ketamine, γ-hydroxybutyrate (GHB), anabolic-androgenic steroids

Opiates / Opioids

The most common drug of abuse under this group is heroin. Its harmful effect arises from the drug itself, its impurities and one of its methods of administration - IV injection. Other methods of use include "chasing the dragon", snorting and subcutaneous administration (skin-popping).

Intoxication effects
Mental: euphoria followed by dysphoria, agitation or retardation and impaired judgment

Physical: pupillary constriction or pupillary dilation (latter due to anoxia from severe overdose), slurred speech, impaired attention or memory, drowsiness and in severe cases, coma

Withdrawal reaction
Runny nose, lacrimation, piloerection, nausea, vomiting, diarrhoea, myalgia, bone pain and insomnia

After-effects
Anorexia, nausea and vomiting, weight loss, respiratory depression, constipation and dependency

Physical effects secondary to IV use
The habit of needle sharing is the main cause of morbidity. The user may develop cellulitis, pustules, vasculitis, thrombosis and myositis. Serious complications include hepatitis, endocarditis, AIDS, sudden death due to respiratory depression or embolism.

Rapid detoxification
While many narcotic drug addicts want to undergo detoxification, traditional techniques, including methadone tapering are usually unsuccessful. The withdrawal syndrome is extremely unpleasant,

may be fatal, and deters patients from completing the detoxification process.

A novel technique called rapid detoxification entails general anesthesia in conjunction with large boluses of narcotic antagonists. This combination allows the individual to completely withdraw from the opiate without suffering the discomfort of the withdrawal syndrome. Unless performed properly, this procedure can be dangerous due to the sympathetic outflow. The procedure is then followed by Naltrexone implant maintenance therapy and professional counselling. Further clinical studies are under way to assess the effectiveness of this treatment.

Cannabinoids

Marijuana, the combined leaves, stems and flowering tops of *Cannabis sativa*, can be used in a variety of forms. It is most commonly smoked via rolled cigarette or in a pipe or bong (water pipe). Hashish, or hash, is the resin obtained from the female plant flowers. It is more toxic than marijuana.

Intoxication effects
Mental: euphoria, relaxation, apparent increase in deep thinking, increased awareness of senses, feeling that boring tasks becomes more interesting, slowness, distorted time perception, tiredness, sleepiness, insomnia.

Physical: impaired motor coordination, conjunctival injection, increased appetite, dry mouth, tachycardia, risk of myocardial infarction (increased for > 4 times in the 1st hour smoking cannabis)

Adverse effects
Anxiety, impaired judgment, social withdrawal, difficulty in following train of thoughts, panic attacks

Withdrawal reactions
Severity of symptoms is related to frequency of use and individual sensitivity. These may last for 1-6 weeks after cessation of use and can include: anxiety, anhedonia, irritability, headache, general discomfort, insomnia, anorexia, craving, feeling of boredom, anger

After-effects
Mental: impairment in concentration, memory, and learning ability, muddled thinking and depression, amnesia, paranoid reaction, hallucination, depersonalization, amotivational syndrome, panic attacks, schizophrenia and dementia-like state, precipitating or exacerbating latent or existing mental disorders, dependency

Physical: respiratory: chronic cough, bronchitis, emphysema, pneumothorax, impairment of immune system, cancer of lips, mouth, pharynx, larynx, trachea, bronchi and lung, right heart disease and pulmonary hypertension, decrease testosterone, sperm count and motility, disruption of the female reproductive cycle, having babies with low birth weight

Drug interaction of cannabis
Cannabis impairs the emesis normally produced by acute alcohol poisoning and can be associated with subsequent alcohol toxicity. It can induce vasodilatation of the nasal mucosa and attenuates the vasoconstrictive effects of cocaine and thus increases its absorption.

Methamphetamine

Methamphetamine ("ice") comes in the form of powder or crystals. It is used locally by the filtering method.

Intoxication effects
Mental: euphoria, hypervigilance, anxiety, tension, anger, insomnia, impaired judgement, panic attacks, paranoid state, psychosis, aggression, self-destructive behaviour

Physical: tachycardia, pupillary dilation, hypertension, sweating, nausea and vomiting, psychomotor agitation, chest pain, myocardial infarction, cardiac arrhythmia, heart failure, stroke, seizure

Withdrawal reactions
Depression, anxiety, irritability, agitation, craving, fatigue, hypersomnia, hyperphagia, loss of energy, loss of interest, suicidal idea

After-effects
Mental: paranoid state, psychosis, dependency

Physical: weight loss and malnutrition, fatigue, stereotype behaviour, dyskinesia, and chorea, cerebral vasculitis, cardiomyopathy

Cocaine

The major routes of administration of cocaine ("coke") are sniffing or snorting, injecting, and smoking the free-base (crack cocaine).

Intoxication effects
Mental: arousal, euphoria, increased energy level, insomnia, irritability, anxiety, fear, restlessness, aggressive behaviour, panic attack, delirium, and acute psychosis

Physical:

- Central Nervous System: headache, stroke, transient neurological deficit, subarachnoid haemorrhage, seizures, toxic encephalopathy, coma
- Respiratory: pulmonary oedema, respiratory arrest, "crack lung" (fever, pulmonary infiltrates, bronchospasm, eosinophilia), pneumothorax, pneumomediastinum
- Cardiovascular: hypertension, aortic dissection, arrhythmia, shock, sudden death, myocarditis, myocardial infarction, other organ ischaemia
- Metabolic: hyperthermia, rhabdomyolysis, renal failure, coagulopathy, lactic acidosis

Withdrawal effects
Craving, paranoia, hunger, suicidal idea, irritability, loss of sex drive, apathy, insomnia or excessive sleepiness, depression

After-effects
Mental: restlessness, insomnia, anxiety, weight loss, hyperexcitablilty, schizophrenia-like psychosis, paranoia, dependency, irritability

Physical:

- Reproductive/neonatal: spontaneous abortion, placental abruption, placenta previa, intrauterine growth retardation, "crack baby syndrome" (irritability, tremulousness, poor feeding, hypotonia or hypertonia, hyperreflexia), cerebral infarction
- Infection: HIV or AIDS, hepatitis B and infectious endocarditis associated with injection; frontal sinusitis with brain abscess associated with chronic cocaine snorting.
- Others: atrophy of nasal mucosa, necrosis and perforation of the nasal septum

Drug interactions
Cocaine abusers use alcohol to potentate cocaine euphoria. Interestingly, the same drug combination has been reported to have been used so that alcohol would counteract the effects of

insomnia and irritability induced by cocaine.

Benzodiazepines

There are a number of benzodiazepines (benzos) commonly abused in Hong Kong, eg diazepam (Valium), flunitrazepam (Rohypnol), midazolam (Dormicum), chlordiazepoxide (Librium), nitrazepam (Mogadon), triazolam (Halcion), nimetazepam ("give-me-five"), estazolam, bromazepam (Lexotan), clozazepam (Rivotril), lormatezepam (Loramet), lorazepam (Ativan or Loran) and dalmadorm (Dalmane).

Intoxication effects
Mental: labile mood, impaired judgment and inappropriate sexual or aggressive behaviour

Physical: sedation, disorientation, slurred speech, ataxia, nystagmus, hypotension and hypothermia

Withdrawal reactions
Mild cases closely resemble an anxiety state. Severe withdrawal reactions include delusion, loss of consciousness and convulsion.

After-effects
Amnesia and dependency

Out-patient treatment for benzo dependence
Withdrawal methods for treating long-term prescribed therapeutic dose benzo users are well established and consist mainly of slow dosage tapering over weeks or months in an outpatient setting, combined with psychological support (Lader and Morton 1991: Ashton 1994). These methods are not entirely appropriate for high-dose benzodiazepine abusers. First, benzo abuse is often part of polydrug abuse and attention also has to be given to the primary drug (usually heroin). Second, a long period of outpatient dosage tapering is unlikely to be adhered to since additional benzos may be obtained illicitly. On the other hand, benzo abusers commonly use high doses and may be at particular risk of severe withdrawal symptoms including epileptic fits if the drugs are stopped abruptly. Therefore, a moderately rapid, controlled schedule of detoxification in an out-patient, or if necessary in-patient unit, is recommended.

Several methods have been described. The most common technique is substitution of a slowly eliminated benzodiazepine (usually diazepam) for the abused drug followed by dosage tapering over 2 or more weeks (Harrison et al 1984; Scott 1990; Williams et al 1996). Some workers (Ries et al 1989) have advocated the use of carbamazepine (ie Tegretol) as an anticonvulsant in benzodiazepine withdrawal, though its ability to prevent other withdrawal symptoms is doubtful (Ashton 1994).

Longer term outpatient management of benzo abusers is problematic. Some centres have found benzos to be helpful in reducing overall illicit drug use and injecting (Greenwood 1996), and occasionally, benzo use may be adaptive, allowing the opiate abusers to manage on a smaller dose of methadone (Stranget al 1993). However, it is generally inadvisable to prescribe benzos as maintenance treatment for drug abusers without specific plans for medical treatment or behavioural modification (Smith and Landry 1990; Department of Health 1991, 1999; Seivewright and Dougal 1992; Seivewright et al 1993). A possible approach for opiate addicted patients who use benzos to increase the euphoric effects of methadone is to alter the methadone treatment so that individuals feel less need for benzos (Seivewright et al 1993). Alternatively, avoidance of benzos can form part of a contract for receiving a higher dose of methadone or other rewards (Stitzer et al 1982). More importantly, it is clear that many benzo abusers, like prescribed users, suffer from mood or psychiatric disorders. It may be that a flexible, individually tailored approach to benzo and other psychotropic drug prescribing, as well as psychological counselling where practical, would bring the best results.

Unfortunately, the rate of relapse after short-term benzo detoxification is high and further experience is needed to establish the optimal long-term management. Meanwhile, efforts to reduce inappropriate prescribing of benzo in general practice (Buetow et al 1996) may help to decrease the quantity of benzos spilling into the illicit drug market.

Treatment Protocol:

- Spend more time with each patient listening and advising them with regard to their problems of drug dependence and associated mood disorders
- Give out the health education leaflet "濫用藥物知多少"
- Offer symptomatic treatment accordingly
- Treat the associated mood disorder

Imidazopyridine & Cyclopyrrolone

This group includes zolpidem (Stilnox) and zoplicone (Imovane). They are alternatives to benzos for treatment of insomnia.

Zolpidem (Stilnox) is an imidazopyridine with rapid onset, short duration of action and is NOT classified as DD in Hong Kong. It has largely replaced benzos as an hypnotic agent. Its sedative effects are additive with alcohol. Like short acting benzos (eg Dormicum) it is reinforcing to alcoholics and drug addicts.

Its adverse effects include impairment in memory and psychomotor function, psychotic reactions and delirium. In recent years, there has been increasing in cases of abuse, dependency and acute overdose.

Zopiclone (Imovane), a cyclopyrrolone, has similar pharmacological actions as barbiturates and benzos although differs chemically.

Adverse effects
Bitter taste, agitation, dry mouth, memory impairment, drowsiness, palpitations, psychomotor impairment, nausea, aggression, nightmares, hallucinations, headache

Withdrawal symptoms
Insomnia, fatigue, tremor, anxiety, muscle twitching, anorexia, sweating, restlessness, palpitations, irritability, headache, poor concentration, craving, noise sensitivity, myalgia, convulsions, numbness, delirium

MDMA

MDMA (3,4-MethyleneDioxyMethAmphetamine) is also known as “Ecstasy”, “Adam”, “XTC” and “E”. There are various adulterants being added during the manufacturing process, which can lead to unexpected effects. Some of the adulterants for MDMA tablets found in Hong Kong include:

- ketamine
- sedative-hypnotics: benzos, methaqualone, phenobarbitone, barbitone, amobarbitone
- stimulants: ephedrine, nikethamide, methylamphetamine
- antihistamines: promethazine, chlorpheniramine, diphenhydramine
- antipsychotics: chlorpromazine, clozapine
- antidepressants: imipramine, clomipramine
- analgesics: paracetamol, antipyrine

- bronchodilators: theophylline, dyphylline
- anticholinergics: benzhexol
- antitussives: carbetapentane

Intoxication effects:
Mental: feeling of relatedness to others, increased empathy, euphoria, increased awareness of senses and decreased aggression, reduced defensiveness, increased awareness of emotion and altered perception of time

Physical: teeth-grinding, tremor, tightening of jaw, gooseflesh, anorexia, increased or decreased body temperature, hyponatraemia due to excessive water intake, sweating, changes in blood pressure, dehydration, tachycardia, hot flushes

Adverse effects
Mental: anxiety, confusion, disinhibition, paranoid psychosis, perceptual distortion, reduced ability and desire to perform mental tasks, increased libido but diminished sexual ability,
Physical: arrhythmia, coagulopathy, acute renal failure, liver toxicity, neurotoxicity, intracerebral haemorrhage, rhabdomyolysis, disseminated intravascular coagulation

Withdrawal reactions
Nil

After-effects and hangover symptoms
Depression, drowsiness, anxiety, panic attacks, aggressive outbursts, psychosis, memory disturbance, impairment of attention, flashback, fatigue, lack of motivation

Drug interactions
MDMA and dextromethorphan can lead to serotonin syndrome, which is characterized by muscle spasm, gastrointestinal problems, confusion, agitation, incoordination, shivering, fever and sweating.

People on SSRI showed a reduced response to MDMA. Those taking MAOI should never take MDMA as this can lead to hypertensive crisis and possibly death.

Ketamine

Ketamine, also known as "Special K", "Super K", "Vitamin K", or just plain "K", is primarily used by paediatric surgeons and anasthetists as an anaesthetic agent with good analgesic effect. The powder is usually snorted while "K tablets" are taken orally.

Intoxication effects
Mental: mood elation, paranoid delusion, anxiety, hallucination, insomnia, impaired attention and learning, calmness, vivid dreams, psychic numbness, delirium, dissociative effect, violence, distorted perception of body, environment and time, suicide, illusion, catatonic state known as K-hole, floating sensation, near death experience

Physical: tachycardia, slurred speech, hypertension, increased intracranial pressure, nausea and vomiting, increased intraocular pressure, hypersalivation, lethargy, numbness, ataxia, incoordination, analgesia

Withdrawal reactions
Fatigue, irritability, poor sleep and depression

After-effects
Cognitive deficits(eg impairment in executive function, memory, attention and learning), soft neurological signs (esp in motor coordination and sensory integration), schizotypal symptoms,

schizophrenia-like psychosis, perceptual distortion and flashback, dependency.

Screening Questions

The aim of screening questions is to alert the doctor to any possible substance abuse problems their patients may have. It is more important for physicians to pick a screening tool and use it routinely than to try to find the best screening method in each situation. There are a lot of screening tools available, but the CAGE questionnaire and the Conjoint Screening Test are the most practical for family physicians. Requiring about one minute to complete, CAGE is a mnemonic for a questionnaire that asks about attempts to:

- **C**ut down on drinking/drug abuse
- **A**nnoyance with criticisms about drinking/drug abuse
- **G**uilt about drinking/drug abuse, and
- using alcohol/drug(s) as an **E**ye opener

The CAGE questionnaire does not differentiate between current and former alcoholism. Screening for other substances can be incorporated into the CAGE format by simply including references to them in the questions. The CAGE questionnaire is thought to be 60-90% sensitive when > 2 questions are positive and 40-60% specific for excluding substance abuse.

The Conjoint Screening Test is even shorter, involving only 2 questions:

- "In the past year, have you ever drunk or used drugs more than you meant to?"
- "Have you felt you wanted or needed to cut down on your drinking or drug use in the past year?"

When primary care patients were studied, at least one positive response detected current substance-use disorders with nearly 80% sensitivity and specificity.

Prescribing DD

Most of us are well conversant on the pharmacological use of DD. It is the psychosocial aspect of DD prescription that has generated a lot of conflicts and stresses among doctors and patients.

Take prescribing benzos as an example. A difficult situation could arise when a regular benzo addict visits our clinics so frequently that the doctors are not sure whether it is appropriate to comply with the patient's request of prescribing more and more benzos. A common excuse for these addicts to ask for refill of their benzo prescription within just a few days is that the medications are lost.

Below are a few guiding principles you may fall back on if you are faced with such a patient:

(1) Any patient can say their medications were lost in space, eaten by dogs, hit by lightning, burnt in hell..., but it is up to the treating doctor to believe their story. If we think there are deeper mental conditions resulting in pathological lying, delusional thoughts, memory impairment...etc, we should refer the patient to a GP with experience in mood disorders and substance abuse, or even to a psychiatrist for further management.

(2) What I usually tell this kind of patient is that, for me to continue to see them and prescribe the necessary medications,

- they need to tell me just how many tablets they REALLY have to take every day,
- they have to promise me that they would keep good custody of the medications, and

- they should not expect me to refill the prescription even if the medications are lost in space, eaten by dogs, hit by lightning, burnt in hell...

(3) Remember to charge the patient a consultation fee each time we see them, and the charge should be commensurate with the time we spend on them.

(5) As doctors we usually comply with our patients' requests as long as the requests are, in our professional judgement, in line with their best interest. However, if a patient's request is, in the doctor's opinion, against the patient's best interest, the doctor should not feel compelled to oblige but should advise that there is a breakdown of doctor-patient relationship, and then offer to refer the patient for a second opinion."

Treatment & Rehabilitation Services

In Hong Kong a multi-modality approach is adopted in delivering treatment and rehabilitation services to suit varying needs of different drug dependent persons.

The public and subsidized drug treatment and rehabilitation programmes include:

- Compulsory placement scheme operated by the Correctional Services Department
- Voluntary out-patient methadone treatment programme provided by the Department of Health
- Voluntary in-patient programmes run by the Caritas - Hong Kong, the Society for the Aid and Rehabilitation of Drug Abusers (SARDA), the Hong Kong Christian Service and other non-government organisations including Christian therapeutic agencies
- Counselling service for psychotropic substance abusers provided by the Caritas - HUGS Centre, PS33 of the Hong Kong Christian Service, Cheer Lutheran Centre and Evergreen Lutheran Centre of Hong Kong Lutheran Social Service and Tung Wah group Hospitals CROSS Centre
- Five substance abuse clinics operated by the Hospital Authority.

There is no accredited centre for treatment of substance abuse in the private sector.

DRUG INTERACTIONS

A large number of drugs are introduced every year, and new interactions between medications are increasingly reported. Multiple drug regimens carry a higher risk of adverse interactions. Precipitant drugs modify the object drug's absorption, distribution, metabolism, excretion or actual clinical effect. NSAID, antibiotics and rifampicin are common precipitant drugs prescribed in primary care practice. Drugs with a narrow therapeutic range are more likely to be the objects for serious drug interactions. Object drugs in common use include warfarin, fluoroquinolones, antiepileptic drugs, oral contraceptives, and statins.

Warfarin

Antibiotics

Almost all antibiotics can potentiate the effects of warfarin by inhibiting intestinal flora that produce vitamin K. Inhibition of the hepatic metabolism of warfarin is another possible mechanism for increased bleeding. Drugs that inhibit warfarin's metabolism include ciprofloxacin (Ciproxin), clarithromycin (Klacid), erythromycin, metronidazole (Flagyl) and trimethoprim-sulfamethoxazole (Septrin).

Unless the INR can be monitored every other day, ciprofloxacin, macrolide antibiotics, metronidazole and trimethoprim-sulfamethoxazole generally should not be prescribed to patients who are taking warfarin. Alternative antimicrobial therapy is recommended for these patients.

Paracetamol

Some investigators advise that the hypothrombinemic response to warfarin can increase when paracetamol is taken in a dosage of more than 2gm per day for longer than one week. The proposed mechanism is a reduced capacity of cytochrome P450 enzymes caused by paracetamol and resulting in decreased metabolism of warfarin.

Because paracetamol is one of the most frequently ingested medications in the Hong Kong, physicians should counsel warfarin-treated patients about the potential risks of a warfarin-paracetamol interaction. If paracetamol therapy is needed, the dosage should be as low as possible, and the drug should be taken for only a short period. In addition, the INR should be monitored closely.

Aspirin

Coadministration of aspirin and warfarin increases the risk of bleeding. The mechanisms of this adverse interaction are antiplatelet effects, gastric mucosal damage and a hypothrombinemic response to warfarin. Several studies have shown that the combination of warfarin and aspirin in a low dosage (75 to 100 mg per day) increases the incidence of minor bleeding, but not major bleeding.

Although concomitant use of warfarin and aspirin generally should be avoided, certain patients may benefit from this therapy. One such group of patients are those with mechanical heart valves or the combination of tissue valves and atrial fibrillation. In these patients the increased risk of bleeding with combined warfarin and aspirin therapy is outweighed by the benefit in decreased thromboembolic events.

NSAID

Taking NSAID and warfarin together increases the risk of bleeding. The mechanisms of this interaction are antiplatelet effect and gastric mucosal damage, because most NSAID do not produce a hypothrombinemic response. When given to or withdrawn from patients maintained on warfarin, NSAID may actually alter anticoagulant control as a result of changes in the amount of circulating

warfarin released from plasma albumin binding sites. Preliminary data suggest that the COX-2 inhibitors may be safer options in patients requiring an NSAID and warfarin, because these agents have reduced antiplatelet properties compared with traditional NSAID.

Concomitant use of NSAIDs and warfarin should be avoided, especially in patients who are at increased risk for NSAID gastropathy. If NSAID therapy is necessary, a COX-2 inhibitior should be used, and the INR should be closely monitored.

Please cross refer to the chapter "Non-Steroidal Anti-Inflammatory Drugs (NSAID)".

Fluoroquinolones

Antacids and iron supplements

Divalent (calcium and magnesium) and trivalent (aluminum and ferrous sulfate) cations can form insoluble complexes in the gut if they are taken concurrently with fluoroquinolones. These cations are readily available over the counter, and patients may not report them as "medicines". Studies have shown that the absorption of fluoroqinolones is reduced by 60-75% when these antibiotics are administered concomitantly with divalent or trivalent cations. Patients should stop taking products containing these cations until fluoroquinolone therapy has been completed. If withholding therapy is not feasible, the fluoroquinolone and cation product should be administered at least 2 hours apart.

Antiepileptic Drugs

Carbamazepine (Tegretol), phenobarbital and phenytoin (Dilantin) are eliminated through hepatic metabolism. Thus, their effects may be potentiated by drugs that inhibit cytochrome P450 hepatic metabolism, such as fluoxetine (Prozac), sertraline (Zoloft), macrolide antibiotics, lovastatin (Mevacor) and azoles.

Rifampin is the "classic hepatic enzyme inducer." When this agent is administered to patients who are taking an antiepileptic medication, increased hepatic metabolism may decrease the serum levels of the antiepileptic drug, possibly resulting in breakthrough seizures.

Serum antiepileptic drug levels should be monitored in suspected cases of drug interactions.

Lithium

Diuretics and NSAID

These alter the sodium balance at the level of the kidney. As a result, serum lithium levels increase secondary to enhanced reabsorption. Some NSAID may also alter prostaglandin effects on the kidney, thereby reducing the elimination of lithium.

If coadministration is necessary, the dosage of lithium should be reduced by 50% when a diuretic or an NSAID is added. Signs or symptoms of lithium toxicity involve the central nervous system (drowsiness, confusion, hand tremor, blurred vision, vertigo and seizures), gastrointestinal tract (nausea and vomiting) and cardiovascular system (arrhythmias and widening of the QRS complex).

Oral Contraceptives

Antibiotics

Rifampicin can increase the activity of hepatic enzymes involved in the metabolism of exogenous

oestrogens. Concomitant use of rifampicin and oral contraceptive pills can lead to breakthrough bleeding and an increased risk of pregnancy. These problems are most likely to occur with formulations containing a low dosage of oestrogen (< 35μg of ethinyl oestradiol).

The interaction between oral contraceptives and other antibiotics is controversial in that no definitive studies have demonstrated contraceptive failure from such combinations. One proposed mechanism is interruption of the enterohepatic circulation of oestrogen as a result of reduced bacterial hydrolysis in the gastrointestinal tract. As a result, patients should be encouraged to consider using an alternative method of contraception for the duration of the cycle.

Sildenafil

Erectile dysfunction is often associated with common chronic diseases such as hypertension, coronary heart disease and diabetes. Therefore, patients with erectile dysfunction are often taking other medications. Sildenafil therapy is absolutely contraindicated in patients who are taking any form of nitrates, because of the potentiation of nitrate hypotensive effects. Sildenafil is primarily metabolized in the liver by cytochrome P450 3A4. Drugs that inhibit this enzyme, including erythromycin, cimetidine, ketoconazole and itraconazole, may increase plasma sildenafil concentrations. Sildenafil therapy should be initiated in the lowest dosage (25 mg) in patients who are also taking a cytochrome P450 3A4 inhibitor.

HMG-CoA Reductase Inhibitors (Statins)

The statins include atorvastatin (Lipitor), rosuvastatin (Crestor), fluvastatin (Lescol), lovastatin (Mevacor), and simvastatin (Zocor). They are metabolized through the cytochrome P450 pathway. Concomitant use of statins and erythromycin, itraconazole, niacin or gemfibrozil (Lopid) can cause a dose-dependent risk of toxicity that manifests as elevated serum transaminase levels, myopathy, rhabdomyolysis and acute renal failure.

Lovastatin may potentiate the effects of warfarin by displacing the drug from plasma protein binding sites or inhibiting hepatic metabolism of the drug. The INR should be monitored in patients who are taking lovastatin and warfarin, especially if the lovastatin dosage is changed.

Selective Serotonin Reuptake Inhibitors (SSRI)

SSRI are generally well tolerated and have a more favorable side effect profile than tricyclic antidepressants. Nearly all SSRI are metabolized by the cytochrome P450 system in the liver. All SSRI except paroxetine (Paxil) have pharmacologically active metabolites.

Tricyclic Antidepressants (TCA)
When concomitant use of an SSRI and a TCA is required, the patient should be monitored for anticholinergic excess. Conservative dosing of the TCA should also be considered.

Tramadol
Tramadol (Tramol) is a centrally acting analgesic with two modes of action: weak binding to the μ-opiate receptor and inhibition of norepinephrine and serotonin reuptake. Reports of serotonin syndrome in association with tramadol and SSRI coadministration appear in the literature. Because depression and chronic pain syndromes frequently coexist, physicians are likely to encounter situations in which this combination is used.

Triptans
A recent report documented six cases of serotonin syndrome in patients taking fluoxetine and

sumatriptan (Imigran). A conservative approach would be to avoid SSRI-triptan combinations.

INADVERTENT OVERDOSING

Most cases of inadvertent overdosing occur when several preparations containing a common ingredient are prescribed together as a drug combination (eg Febricol tab 1 qid + Syncofit Co syrup 10ml qid = a total daily dose of 480mg of pseudoephedrine!)

Pseudoephedrine

DRUG	Pseudoephedrine
Became tab	60mg
Codaewon tab	17.5mg
Decofed syr	30mg / 5ml
Febricol RF tab	30mg / 5ml
Fedac (DHA) tab	60mg
Fenfedrin cap	60mg
PEC syr	7.2mg / 5ml
Pseudoephedrine tab 60mg	60mg
Syncofit Compound syr	30mg / 5ml
Telfast D tab	120mg
Triple P cough syr	5mg / 5ml
MAXIMUM DOSAGE:	**Adult = 240mg/d**
	Child [6-12] = 30mg qid (ie 120mg/d)
	Child [2-5] = 15mg qid (ie 60mg/d)

Chlorpheniramine

DRUG	Dexchlorpheniramine	Chlorpheniramine
Antihist tab 2mg		2mg
Antimine syr 2.5mg/5ml		2.5mg/5ml
Chlorpheniramine tab 4mg		4mg
Codaewon tab		1.5mg
Codolax syr		2mg/5ml
Codoplex syr		2mg/5ml
Dex-Antihist tab 2mg	2mg	4mg
Febricol RF tab		2mg
Fenfedrin cap		4mg
Rhiniramine SR tab 6mg	6mg	12mg
Synbetamine cap	2mg	4mg
Synbetamine syr	2mg/5ml	4mg/5ml
MAXIMUM DOSAGE	**Adult**	**24mg/d**
	Child [6-12]	**12mg/d**
	Child [2-5]	**6mg/d**
	Child [1-2]	**2mg/d**

The mnemonic, "dry as a bone, red as a beet, hot as a hare, mad as a hatter, and blind as a bat," summarizes the classic combination of central and peripheral anticholinergic effects of antihistamine poisoning. Other manifestations of toxicity, such as seizures, cardiac arrhythmias, and hypotension, are not uncommon and may be explained by mechanisms other than anticholinergic effects.

Terfenadine

Although terfenadine (Histafen) toxicity, including the potentially life-threatening torsades de pointes arrhythmias, occurs when it is taken with azoles like ketoconazole, itraconazole and miconazole, it does not seem to occur when taken with normal doses of fluconazole (200mg daily). Ketoconazole (even in topical usage) and itraconazole appear to reduce hepatic metabolism of terfenadine through inhibition of cytochrome CYP3A. Grapefruit juice contains a chemical which inhibits the same enzyme and may cause the same life-threatening arrhythmias when taken with terfenadine. The same applies to those macrolides (especially erythromycin, clarithromycin) which inhibits P450 as well. Although also a macrolide, azithromycin (Zithromax) can be safely taken with terfenadine.

Fexofenadine (Telfast) will not produce cardiac arrhythmias when taken with azoles, and has largely replace terfenadine as a useful second generation H1-blocker.

INTRAMUSCULAR INJECTIONS (IMI)

Intramuscular injection is an invasive form of treatment. If there is an alternative oral medication, then this may be the safer route to take. Although a lot of medicines can be administered through the intramuscular route, NSAID (eg diclofenac) and steroids appear to be involved in most cases.

For many years the Medical Protection Society has advised its members to use, unless otherwise recommended by the manufacturer of the medications to be administered, the antero-lateral side of the thigh (the vastus lateralis) for intramuscular injections to avoid damage to the sciatic nerve.

If an intramuscular injection is to be given to the buttock, the following 3 points have to be observed:-

1. The injection must be given to the upper outer quadrant.
2. The patient must be standing up straight or lying prone.
3. The injection must be deep enough to reach the gluteal musculature.

Complications

Depending on different studies, IMI carries a complication rate in the range of 0.5-20%.

Leakage
This usually occurs in a patient who has significant scarring at the injection site, which makes the tissue hard and less receptive to accepting the volume of injected fluid.

Bleeding
Significant bleeding and haematoma formation can occur if blood vessels are injured. IMI should be avoided in anticoagulated patients. Patients on antiplatelet agents including aspirin should be watched closely following an IMI to identify any bleeding problem.

Necrosis
It has been found that muscular necrosis will occur after any IMI no matter what medication is injected. The only variable is the size and the severity of the necrotic lesion. Forceful placement of a volume of fluid into a closed space will cause pressure necrosis. The kinds of the medication (esp NSAID, antibiotics, steroids and some long-acting preparations), the volume injected, and even the injection speed will influence the size of the necrotic lesion.

Nerve injury
Any nerve in the vicinity of the chosen injection site is likely to be damaged. The radial nerve is likely to be injured with injections in the deltoid or upper arm areas. The sciatic nerve is commonly injured by gluteal injections, especially in children. Sciatic nerve injury following injection is commonly manifested by paresis in the sciatic distribution followed by a causalgia or burning pain in the extremity several hours or days later. Radial nerve injury at the shoulder may be manifested by paraesthesias in the distribution of the radial nerve and wrist drop. Recent information has shown there is no specific medication that is neurotoxic when injected close to a nerve, but all will result in necrosis of the nerve if injected intra-neurally.

Persistent pain
The prolonged pain can be due to irritation or chemical neuritis of a nerve, and local muscle spasm. Continued pain at an IMI site must be investigated to ensure it is not a symptom of an underlying abscess or other local problem. Many times this requires an MRI scan of the area. It is of interest that neither needle size nor needle length influences the degree of pain experienced at the time of the injection or the incidence of post-injection persistent pain.

IV injections
Almost none of the medications given by the IM route are safe to be given intra-arterially. The majority of the reported cases of inadvertent injection of medication into arteries during attempted IMI occur in children receiving injections in the buttock region. This results in a severe chemical injury to the vessels with vasospasm and thrombosis. Skin necrosis, neurological damage, and loss of limb can follow. Unfortunately, aspirating the syringe prior to injection of the medication to see if there is blood return does not guarantee that this problem will not occur.

Abscess formation
Infectious abscesses following IMI are caused by the inoculation of the site with bacteria from the needle, syringe, or the medication. The majority of these cases are seen within a few days to a few weeks following the injection; however, in some cases, an abscess clinically may not be apparent for years after the injection. A high index of suspicion must be maintained for uncommon infectious problems after an injection, especially in the immunocompromised patient.

More commonly, the abscesses that are seen at IMI sites are sterile abscesses. These are nodules of liquefied fat and muscle resulting from necrosis of the involved tissues. When the medication is injected into the subcutaneous tissues rather than the muscle, absorption is delayed, which allows for a greater tissue reaction to the medication. This reaction is manifested by local tissue necrosis and liquefaction with a surrounding area of intense inflammation. Thus, a painful nodule filled with sterile, liquefied tissue remains at the site. Many times this problem is caused by not using a needle of sufficient length to reach the muscle.

Scar formation
If multiple injections are given, especially in the same area over a protracted period of time, the areas of necrosis may become quite large and result in large areas of fibrosis of the tissues. This may be manifested by hard nodules felt deep in the tissues and even sunken areas of scar tissue seen on the surface of the skin. Dystrophic calcification of the scar tissue can occur with time resulting in even more painful areas.

Joint contracture
Numerous reports have shown that fibrosis of the extremity muscles following IMI can result in contracture of joints. The local damage caused by the injected medication together with pressure necrosis causes the muscles to scar and shorten, thus resulting in joint contractures.

Malignancy
The reported tumours have all been forms of sarcoma. There has not been a common medication injected in patients who developed the malignancies. Even though the incidences are extremely low, any patient who has had an IMI and continues to complain of a painful nodule at the injection site well after the injection should be thoroughly examined.

Prevention of Complications

Manufacturers' instructions
These are written for a purpose and will be the standard by which the courts will judge us should a medico-legal situation arise. If we deviate from them we must have a very good reason for doing so and there must be a responsible body of medical opinion to support our decision.

Alternative route of administration
Since all IMI cause necrosis of the tissues and some type of reaction, **avoiding the technique if possible** is probably the best strategy to prevent complications associated with IMI.

Informed consent
Those patients who press for a poorly indicated IMI should be given a detailed presentation of the

above potential complications. In this regard it is worth noticing that most developed countries (including the HKSAR) are moving towards the American doctrine of informed consent and what is known as the 'prudent patient test'. This means that there is no liability on the doctor's part if any prudent person in the patient's position would have accepted the treatment had they been adequately informed of all significant possible risks. These range from common risks with minor effects to rare risks of major significance. The crucial element here, of course, is the significance that different patients might place on those risks, depending on their characteristics and personal circumstances.

Injection site

To avoid neuro-vascular complications, the approved landmarks for the injection site should be identified whether in the deltoid, the gluteal, or the lateral thigh regions.

- Deltoid: This may work well for a person with developed muscles in the upper body. In general the deltoid region should only be used in vaccination (eg hepatitis shots).

- Gluteal: The upper outer quadrant of the buttock is probably the most chosen area or IMI. One should never give an IMI to the gluteal region with the patient in a sitting position. One should also avoid using this region in infants or children under 3 years old because the dorso-gluteal muscle is not developed well enough.

- **Lateral thigh: This is the safest, and the recommended site for most patients including the elderly and the infants.**

Injection techniques

To avoid injecting the medication into the subcutaneous tissues, it is imperative that a needle of appropriate size and length be used.

Techniques to avoid inadvertent intravascular injection of medications have not been routinely successful. The traditional "withdrawal" technique is the best available but in no way foolproof. The needle could be within the vessel lumen but against the distal wall, which seals the needle tip during aspiration. However, once injection begins, the medication unfortunately can be easily deposited within the lumen of the vessel. Repositioning of the needle tip after aspiration and before injection can result in inadvertently entering the lumen of an adjacent vessel. Care must be taken to make all reasonable efforts to avoid this complication since the results can be devastating.

Alternating site

Alternating the injection site can prevent complications from tissue necrosis. Repeated injection of any medication into the same area will increase the size of the necrotic lesion.

Delegating duty

When delegating any task to a CSA (or any other persons for that matter), we must ensure that she is competent to carry it out and fully acquainted with the appropriate techniques or methods. Before a patient can give valid consent to an injection they must be told who will be administering it. Otherwise they can claim that the consent was invalid; this means that the CSA who gave the injection could face criminal charges of assault, battery or worse. In addition, we could also face criminal charges, a complaint to the medical council or a claim in negligence.

Repeated IMIs

Every now and then a patient approaches us requesting for long-term regular out-patient analgesic injections. Although sometimes we need to give parenteral analgesics to our patients in the clinic, I cannot think of any clinical indications of giving long-term regular pain-killing shots on an out-patient basis.

I believe most of these requests come from patients who have been given regular NSAID or even

narcotic injections in some other clinics. A good proportion of them may also be taking other augmentation drugs like analgesics, anxiolytics, or anti-depressants…etc.

To handle such patients, one must first take a careful medical history and perform an adequate physical examination to look for, among other things, clinical features of the alleged condition resulting in persistent pain, and evidence of any complications resulted from repeated intramuscular or intravenous injections.

If there is a physical illness necessitating regular analgesia, one should first consider regular paracetamol 1gm PO qid. This is not only extremely safe but also surprisingly effective. The combined dosage form of paracetamol 325mg and dextropropoxyphene 32.5mg (eg Dologesic) has not been shown to be more effective than a paracetamol tablet of 500mg. NSAID and the newer COX-2 agents offer alternatives for oral analgesics. A new product, Spedifen (ibuprofen arginine 400mg), seems to be promising in terms of safety and efficacy.

For patients suffering from conditions that require long-term narcotic analgesia, one should consider oral morphine. The syrup form is easy to use and titrate by both the doctors and the patients. A reasonable starting dose is 5mg PO q4h prn. An anti-emetic (eg dimenhydrinate) and a stool softener (eg lactulose) are usually prescribed together to be taken as required.

You may be surprised to know that it is quite uncommon for patients with genuine physical pain to get addicted to narcotics prescribed for therapeutic purpose. A patient who claims that they need long-term regular narcotic injections for a seemingly trivial condition is likely to be a drug addict to start with, and should be managed professionally as one.

What if a patient, after being advised that the injection is professionally unacceptable, still insists that you should give them that injection?

In TY, we talk a lot about "patients" being "customers", and how doctors should go an extra mile to serve their "customers". One may then argue that if a TY customer asks for a service and is willing to pay for it, our doctors should provide it without question. In this regard, one must not forget it is our mission to "apply the highest professional standards to caring of patients and prevention of diseases". In fact, a doctor-patient relationship is much more than a commercial "buyer-seller" relationship. In providing medical services, doctors are required to exercise their own independent professional judgement to act for the best interest for their patients. Therefore, if a patient's request is, in the doctor's professional opinion, against the patient's best interest, the doctor should refuse to comply (*Please cross refer to the chapter "Dangerous Drugs"*).

So, to answer the above question is:

"You should not feel compelled to oblige but should advise that there is a breakdown of doctor-patient relationship, and then offer to refer the patient for a second opinion."

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

NSAID are among the most prescribed medications anywhere in the world. A review of clinical visits and prescriptions in the US however estimated that unnecessary prescriptions for NSAID were written in 40% of cases.

Classification

NSAID can be classified based on their chemical structure, and those within a group tend to have similar characteristics. They act by inhibiting the enzyme cyclooxygenase (COX), which catalyzes arachidonic acid to prostaglandins which establish the inflammatory response. Since all NSAID inhibit the same cyclooxygenases, giving 2 or more of them together does not increase the efficacy. Instead, it increases the risks of adverse drug reactions. A paracetamol-NSAID combination may be useful because paracetamol probably acts on COX-3 as mentioned below. There is little difference in clinical efficacy between different NSAID when used at equivalent doses. Rather, differences between compounds are with regards to dosing, routes of administration, and side effect profiles.

Traditional NSAID

- Salicylates (aspirin)
- Arylalkanoic acids (diclofenac, indomethacin)
- Profens (ibuprofen, naproxen)
- Fenamic acids (mefenamic acid)
- Oxicams (piroxicam)
- Coxibs (celecoxib, parecoxib, etoricoxib)
- Sulphonanilides (nimesulide)

Paracetamol

This very popular OTC drug, owing to its inhibitory action on cyclooxygenase, is sometimes classified as an NSAID. However, it does not have any significant anti-inflammatory properties and is not a true NSAID. It is suspected that paracetamol inhibits predominantly the CNS cyclooxygenase, thus having virtually zero anti-inflammatory action. There is also some speculation that paracetamol acts through the inhibition of the recently discovered COX-3 isoform.

COX-2 inhibitors

- The newer, more selective COX-2 inhibitors like nimesulide (Nidol), celecoxib (Celebrex), and etoricoxib (Arcoxia) cause less serious GI toxicity, compared to traditional NSAID.
- COX-2 agents seem to be associated with a higher cardiovascular risk.
- Unlike their COX-1 counterpart, COX-2 agents do not have any anti-platelet property.
- Parecoxib (Dynastat) is the world's first intravenous COX-2 agent. The maximum daily dosage is 40mg q12h iv. With its introduction the use of Toradol and Tramol is expected to decline.

NSAID-induced Gastropathy

The side effects of NSAID are usually dose- and duration-dependent. About 10-20% of patients taking them experience dyspepsia, and NSAID-associated gastropathies are believed to result in roughly 40% of drug-related emergency visits in the USA.

General considerations

Approximately 50% of patients on regular, long-term NSAID treatment have NSAID-induced gastropathy characterized by subepithelial hemorrhages, erosions, and gastric ulcers (GU). Most of these patients are asymptomatic. The risk factors for NSAID-associated GU include:

- Age > 60
- Past gastric ulcer
- High dosage of NSAID
- COX-2 agent plus aspirin

Although some authors have suggested that NSAID cause a diffuse chemical or reactive gastritis, this has not been clearly documented in studies involving pre- and post-treatment biopsies.

NSAID cause a dual insult on the GI tract - the acidic molecules directly irritate the gastric mucosa; and inhibition of COX-1 reduces the levels of protective prostaglandins. COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes. One of these is in the stomach lining, where prostaglandins serve a protective role, preventing the stomach mucosa from being eroded by its own acid. When non-selective COX-1/COX-2 inhibitors (such as aspirin, ibuprofen, and naproxen) lower stomach prostaglandin levels, these protective effects are lost and gastropathies can result. COX-2 is an enzyme facultatively expressed in inflammation, and it is inhibition of COX-2 that produces the desirable effects of NSAID.

There are some differences in the propensity of individual agents to cause GI side effects. Among the more commonly used NSAID, ibuprofen causes the least, and aspirin, diclofenac, naproxen, indomethacin, piroxicam cause more gastropathy, in ascending order.

Basic principles

- There is NO correlation between NSAID gastropathy and upper abdominal symptoms frequently experienced by patients taking NSAID.

- Most patients on short-term NSAID treatment do not need any stomach protection. It has been estimated that < 1% of patients taking NSAID for 6 months develop clinically significant gastric complications.

- **If a patient is not suffering from active peptic diseases, NSAID can safely be taken after meals. If the patient does have active peptic diseases, then NSAID should not be given at all. Alternative analgesics, eg narcotics, should be considered.**

- Cosalgesic (dextroproproxyphene* and paracetamol, also marketed as Dologesic) is NOT an NSAID; it causes upper GI complications no more than paracetamol alone.

- **Although antacids can heal duodenal ulcers, they are of unproven value in treating GU, and have no place in preventing NSAID-induced GI damage.**

- Stomach mucosal anaesthetics (eg Strocain) do NOT protect the stomach from NSAID-induced damage. They may even delay the presentation and treatment of NSAID-induced gastropathies by masking the relevant symptoms.

- Misoprostol (Cytotec), H2 antagonists (eg famotidine 40mg bd), proton pump inhibitors (eg esomeprazole 20-40mg qd) are significantly more effective than placebo in the prevention of both gastric and duodenal ulcers associated with long-term, regular use of NSAID. Misoprostol may cause diarrhoea.

** In February 2009 the US FDA advisors recommended propoxyphene be pulled from the US market in view of*

its adverse-event reports that involved suicides, intentional and unintentional drug overdoses, and heart attacks.

Non-GI Adverse Effects

Like the GI side effects of NSAID, these are also dose- and duration-dependent in general.

Renal side effects
These are probably due to changes in renal haemodynamics (mediated by prostaglandins, affected by NSAID), and include salt and fluid retention, hypertension as well as renal impairment. The risk is higher if the patient is also concomitantly taking an ACEI and a diuretic - the so-called "triple whammy" effect. In rare instances NSAID may also cause more severe renal conditions like interstitial nephritis, nephrotic syndrome and even acute renal failure.

Cardiovascular risk
A recent meta-analysis found an 80% increase in the risk of MI with both newer COX-2 antagonists and high dose traditional NSAID compared with placebo (Kearney et al., BMJ 2006;332:1302–1308). NSAID are associated with a 2-fold increase in heart failure in patients without a history of cardiac disease. In patients with such a history, however, use of NSAID (besides low-dose aspirin) was associated with more than 10-fold increase in heart failure.

Asthma
Aspirin-exacerbated respiratory disease (AERD) is a subtype of asthma characterised by asthma and rhinitis triggered within 1-3 hours of ingestion of aspirin and other NSAID. The initial onset of symptoms appears at an average age of 30 years, with rhinitis characterised by persistent watery rhinorrhoea, nasal obstruction and sneezing. Loss of a sense of smell, with development of troublesome nasal polyps, occurs in up to 2/3 of patients. On average, asthma develops 2 years after the onset of rhinitis, with intolerance to aspirin and other NSAID occurring about 4 years later.

3-8% of asthmatics are hypersensitive to aspirin and other NSAID who may develop life-threatening bronchoconstriction if exposed to NSAID. **NSAID are therefore relatively contraindicated in patients with a history of asthma, and absolutely contraindicated in active asthmatics.**

Other side effects
Photosensitivity, raised liver enzymes, headache, dizziness, hyperkalaemia, and confusion.

NSAID in URTI

NSAID are of unproven value in reducing upper respiratory mucosal inflammation in URTI. The common association of URTI and allergic symptoms (nose and/or airways) actually makes prescribing NSAID therein more undesirable. For relief of pain and fever, paracetamol is a safe and effective choice (and don't forget the codeine contained in cough suppressants is a narcotic analgesic).

Pregnancy

NSAID are generally not recommended during pregnancy. While they as a class are not direct teratogens, they may cause premature closure of the ductus arteriosus and renal adverse reactions in the foetus. Additionally, they have also been linked with premature birth. In contrast, paracetamol is regarded as being well-tolerated during pregnancy.

COX-3 Inhibitors

COX-3, discovered in 2002, has been analyzed in relation to paracetamol, arguably the most widely used analgesic drug in the world. The researchers postulated that inhibition of COX-3 could represent a primary central mechanism by which these drugs decrease pain and possibly fever.

PSYCHOTROPIC DRUGS & PREGNANCY

Pregnancy carries a baseline spontaneous abortion rate of 7–8% and teratogenicity of 2–4%. A drug administered during pregnancy may cause somatic or neurobehavioural teratogenicity. On the other hand, the teratogenicity and other functional morbidities (to the mother and child) caused by the untreated illness itself must also be considered.

Depression in Pregnancy

10-16% of women suffer from minor or major depression during pregnancy, some of them evolving into post-partum depression. A recent study has shown that pregnant women with major depression have a 26% relapse rate if they are maintained on medication, but the relapse rate increases to 68% if their medication is withdrawn. If left untreated, depressed pregnant women are more prone to suffer from miscarriages, hypertension, pre-eclampsia and post-partum depression. The foetus will also be adversely affected, showing slow foetal growth, smaller infant head circumference, preterm delivery, low Apgar score and other obstetric complications. The infant is also pre-disposed to long-term neurobehavioural changes which may persist into adulthood.

Antidepressants are known to increase the rate of spontaneous abortion. For bupriopion (Wellbutrin), the rate is 15.4% (statistically significant), for selective serotonin reuptake inhibitors (SSRI) the rate is 13.5% and for tricyclic antidepressants (TCA) it is 10.7%, with a control of 7–8% in normal pregnancies. Antidepressants are also known to cause low birth weight and preterm birth.

TCA

TCA do not cause excessive teratogenic effects, or neurobehavioural adverse effects, so it is a relatively safe group to use during pregnancy. The dose is usually raised later in pregnancy, gradually to about 1.6x normal dose, to cater for the increase in body weight. As pregnant women are more prone to orthostatic hypotension, a drug is selected to avoid this side effect. It is also necessary to avoid the anticholinergic actions causing toxicity in the neonate, which include functional bowel obstruction, urinary retention, constipation and tachycardia. With these considerations, nortriptyline (Nortrilen) is the drug of choice. TCA are generally safe in lactation, but doxepin has been reported to cause respiratory depression with high blood levels detected.

SSRI

It has been observed that infants born to mothers taking SSRI towards the end of pregnancy suffered from adverse events that were about 3x as frequent as controls. These complications are, fortunately, usually mild in nature.

A recent study reported a 6x increased risk of persistent pulmonary hypertension of the newborn, a severe and potentially fatal condition, in infants exposed in utero after week 20. In a Danish cohort study, the estimated relative risk of all congenital malformations, compared with the general population, among the offspring of women who received a prescription for an SSRI was 1.4 and the relative risk of cardiac malformation was 1.6. An American retrospective study, 4% of the newborns exposed to paroxetine (Seroxat) had malformations (2% had cardiac malformations). The estimated relative risk for all congenital malformations was 2.2.

Newer Antidepressants

A case series of 21 women using newer antidepressants mirtazapine (Remeron), nefezodone (Serzone) and venlafaxine (Efexor) during the first trimester of pregnancy did not reveal any increase in teratogenicity. There have been reports of detectable levels of venlafaxine and its metabolite in breast-fed infants. No immediate or subsequent neurobehavioural adverse effects were found.

Management of Depression in Pregnancy

Counselling should start before a planned pregnancy. The patient should be guided towards a balanced and realistic view of the risks involved. Before conception and during the first trimester, the physician should review the need to continue medication. The regime should be simplified to avoid polypharmacy, and drugs should be given at the lowest dosage possible. The safest medication should be chosen, for example nortriptyline (FDA Category C) if a TCA is used, and fluoxetine (Prozac) if an SSRI is prescribed. Drugs that are least preferred should be stopped, as with bupropion and paroxetine. Some physicians may deem it possible and appropriate to stop antidepressants in the first trimester, with a view to resuming medication later. In such cases the patient should be followed closely for any relapse of symptoms. In the second and third trimester, it is also necessary to gradually increase the dose of the drug, to 1.6x normal dose, to take into account the gain in weight of the mother. However, the dose of drugs should be gradually reduced, say from 2 weeks towards confinement, to avoid toxic or withdrawal effects in the neonate, with plans to reinstate the drug after delivery.

Lactation

In the nursing mother, the SSRI of choice are fluvoxamine (Faverin) and paroxetine, followed by sertraline (Zoloft). Fluoxetine and citalopram/escitalopram (Cipram/Lexapro) should be avoided. This is guided by the drug concentration in secreted milk and the blood levels detected in infants.

Benzodiazepines

Benzodiazepines are generally safe in pregnancy. They do not produce long-term neurobehavioural effects in infants. Most benzodiazepines are classified under category D of the FDA Pregnancy Safety Index. **Clonazepam (Rivotril), classified category C, is the benzodiazepine sedative of choice.**

As for benzodiazepine hypnotics, flurazepam (Dalmadorm) and triazolam (Halcion), of category X, should not be used. Flunitrazepam (Rophynol) in category D is a better choice.

For non-benzodiazepine hypnotics, zolpidem (Stilnox) has a B categorization and zopiclone (Imovane) is unknown.

Neonatal toxicity from benzodiazepines must be carefully monitored. This occurs when the mother is taking a high dose of medication, and when the baby is preterm. Signs in the baby are: floppy infant syndrome, hypothermia, lethargy, poor respiratory effort and poor sucking. Neonatal withdrawal syndromes are signified by restlessness, hypertonia, hyperreflexia, tremulousness, apnoea, diarrhoea and vomiting.

Lactation

These drugs are secreted in low levels in breast milk. However, short-acting drugs should be used to avoid accumulation in breast milk, and infants should be observed for possible sedation. Common benzodiazepines preferred or to be avoided are listed below:

	Pregnancy	Lactation
Diazepam (Valium)	Yes	No
Chlordiazepoxide (Librium)	Yes	Yes
Clonazepam (Rivotril)	Yes	Yes
Lorazepam (Ativan)	Yes	Yes

Alprazolam (Xanax)	No	No

Antipsychotics

Typical antipsychotics

These are generally assigned to Category C of the FDA schema. From the chemical structure, they can be divided into low potency compounds such as chlorpromazine (Largactil), or high potency compounds such as trifluoperazine (Stelazine), perphenazine (Triafon) and haloperidol (Serenace). There is a small increase in congenital abnormality in offspring exposed to low potency antipsychotics during the first trimester. Thus low dose of high potency compounds are preferred. Perinatal syndromes are rare. Typical antipsychotics are detected in very low doses in nursing infants, and no ill effects are evident.

Atypical antipsychotics

Prospective studies are rare. McKenna et al observed the effect of olanzapine (Zyprexa), quetiapine (Seroquel), clozapine (Clozaril), and risperidone (Risperdal), and concluded that there is no statistical difference in the rate of miscarriages, stillbirths, prematurity, congenital malformation and perinatal syndromes compared to controls. Clozapine should not be prescribed to nursing mothers.

Lithium

This is frequently used in bipolar depression or to augment antidepressants. Rapid discontinuation of lithium over 2 weeks is associated with a 63% relapse rate, and a more gradual discontinuation over 1 month is associated with a 37% relapse rate. Also, during pregnancy, a significant reduction in lithium level is associated with a 50% relapse rate, and no change in lithium level is associated with a 20% relapse rate.

Views regarding the teratogenicity of lithium have undergone some changes over the years. When the drug was first introduced in the sixties, it was observed to produce a 400-fold increase in the incidence of Ebstein's anomaly, a congenital defect involving the tricuspid valve. Later studies detected a much lower figure of 10–20 times. The most recent studies revealed no excess in cardiac teratogenicity. In pregnant women, a decision is often made whether to discontinue lithium in the first trimester. This will depend on the history and symptoms of the patient, and the likelihood of relapse on withdrawal. During pregnancy, frequent foetal echocardiogram and foetal ultrasound are necessary to detect any congenital malformation. Repeated blood monitoring is required due to the continuing change in physiological status of the patient. Lithium has not been found to adversely affect neurobehavioural development. The incidence of perinatal toxicity is low. Lithium is contraindicated in nursing mothers as it can reach toxic blood levels in the baby, with lethargy, hypotonia, hypothermia, cyanosis and ECG changes.