How Stoke-on-Trent is keeping its prescribing budget under control

Gareth Malson and Lin-Nam Wang talk to the head of medicines management at NHS Stoke-on-Trent, about incentive schemes to change prescribing behaviour and how switching from a macro- to micro-management system can lead to better control of resources

Traditionally, the main financial concern of primary care organisation (PCO) chief executives has been whether or not their trusts will finish the year within budget. Having such an overarching view ensures the organisation remains financially viable, but does it also make sure taxpayers are getting the best “bang for their buck”?

Andrew Riley, head of medicines management at NHS Stoke-on-Trent, believes that the drug budget needs to be broken down into manageable chunks to allow practices to deliver the most cost-effective prescribing. “Because the PCO budget is so large, overspending in one therapeutic area can be masked by underspending in another,” he says. “Therefore, there is an element of chance as to whether budgets are met. A lot can be hidden if you’re dealing with a single figure of £60 million.”

He explains that formulas produced by the NHS Prescribing Support Unit can be used to predict increases in PCO drug expenditure. However, with the NHS expected to experience extra financial pressure over coming years, this method may need to evolve. “Macro-managing prescribing budgets at PCO level has worked in the past, but it’s not sufficient any longer. Now, PCOs need to micromanage their budgets at individual practice level,” he proposes.

NHS Stoke-on-Trent has altered the way it monitors the prescribing of its GP practices by introducing what it calls “prescribing programme budgets”. Mr Riley told The Journal that his approach is based on the economic concept of programme budgeting and marginal analysis, which is recommended for use in commissioning and redesign of services, helping to align the goals of doctors and managers. “It is a well established way to maintain control,” he says.

The Stoke approach focuses on the main components of the trust’s total drug budget with the rationale that if these can be monitored, most of the budget will be managed. This also allows practices, and practice-based commissioning (PBC) clusters (of which there are five within the PCT), to scrutinise their prescribing habits more easily, with emphasis on the key therapeutic areas. So in 2008, NHS Stoke-on-Trent identified five groups of prescribed medicines as an emergency supply, as a result of new legislation. They can now also make an emergency supply at the request of UK-registered dentists or their patients.

Recent news at a glance

**Cancer**
The first treatment that delays the return of gastrointestinal cancer after surgery, imatinib (Glivec), has received UK approval. In addition, a treatment for advanced hormone-dependent prostate cancer, degarelix (Firmagon), a gonadotrophin-releasing hormone antagonist, has been launched.

**Emergency supply rules**
Pharmacists can now supply up to 30 days’ worth of prescription-only medicines as an emergency supply, as a result of new legislation. They can now also make an emergency supply at the request of UK-registered dentists or their patients.

**Erythropoetins**
A meta-analysis of 50 clinical trials, published in The Lancet, found higher mortality in cancer patients treated with erythropoiesis-stimulating agents (epoietin or darbepoetin) compared with control groups.

**Folic acid**
Fortification of foods with folic acid has been linked with a decrease in the number of babies with congenital heart defects, according to a Canadian study.

**Multiple sclerosis**
The use of methylprednisolone (200mg on five consecutive days, every four weeks) as add-on therapy to interferon beta-1a may reduce the relapse rate in patients with multiple sclerosis, according to a small study in Lancet Neurology.

**Thromboembolism**
Rivaroxaban administered as a 10mg daily dose starting six to eight hours after knee surgery was found to be more effective at preventing deep vein thrombosis, pulmonary embolism and death than 30mg subcutaneous enoxaparin, according to a study in The Lancet. Oral regimens could enable shorter hospital stays.
Learning & Development

PRESCRIBING AND MEDICINES MANAGEMENT

“prescribing programme” with its own budget. To help keep these programme budgets on track, the PCT provides each practice (and cluster) with a monthly breakdown of its prescribing expenditure.

Big ticket drugs
Antibiotic formulary compliance is also highlighted, along with seven other targets for formulary compliance — drugs that the trust has identified as the most cost-effective in their therapeutic area. These are:

- Omeprazole and lanzoprazole
- Benidromethiazide
- Ramipril, lisinopril and perindopril
- Simvastatin 10, 20 and 40mg and all pravastatin strengths
- Loratadine and cetirizine
- Citalopram
- Alendronic acid

Mr Riley adds that clusters and practices are encouraged to focus efforts on these low cost, high volume drugs “identifying [these] big ticket items helps practices to focus on using cost-effective, evidence-based drugs.” He explains that evidence has stacked up for a long time on many of these drugs, in terms of head-to-head comparisons and the trust uses organisations such as the National Prescribing Centre and the Aggressive Research Intelligence Facility in Birmingham, for decision-making information. His tip for persuading prescribers to change prescribing behaviour is to present them with five reasons, giving a “royal flush” in poker terms. These are national guidance, a strong evidence base, the opinion of a national leader, the opinion of a senior local clinician and some measure that the drug is appropriate for most patients.

Each surgery’s compliance with programme budgets and the trust’s medicines formulary is shown in the monthly breakdown, which Mr Riley describes as a powerful incentive. “The last thing a practice wants is to be an outlier,” he says. Where targets have not been met, the offending surgery’s score is highlighted on the summary sheet in red. Acheived targets are highlighted in green. This allows the cluster to identify prescribing problem areas and compare month-to-month performance easily.

But Mr Riley is keen to emphasise that prescribing programme budgets are more than a spreadsheet or just a new way of presenting the figures. It is a way of thinking — a way of framing questions and objectives of measuring, planning, co-ordinating, networking and reporting. He adds that, within each cluster, a group of leading practitioners should meet regularly to discuss the cluster’s prescribing patterns. Such a group should consist of leading GPs, practice-based commissioning managers, finance representatives, commissioners, and primary care pharmacists and technicians. “Few people at practice level have had financial training,” he says. “With programme budgets in place, this group can identify prescribing issues and plan changes to improve overall cost-effectiveness.”

As part of the new approach, each practice was invited to join a voluntary incentive scheme. “These are contractors and not employees so they cannot be forced and we need to incentivise [them],” Mr Riley explains.

Modifying the model
O ne crudity of the 2008/09 model was that prescribing incentives were offered to practices that achieved one overall financial target. “Prescribing change,” he says. “Mr Riley. This meant that a practice could over-spend in one programme budget, but the target could still be met provided it under-spent sufficiently in another. As a result, practices were not incentivised to deliver maximum financial efficiency in all areas of prescribing. Consequently, for 2009/10, the incentive will be split, with a target attributed to each prescribing programme and practices will need to meet their target in each area to be entitled to the full reward. In addition, a sixth programme budget, covering medicines within the nutrition and blood section of the British National Formulary (with particular emphasis on enteral sip feeds) has been added. “We wanted to increase coverage to 85 per cent,” Mr Riley explained.

Getting prescribers to sign up can be a challenge, and so far there has been mixed early feedback. Figures relating to prescribing programmes budgets are due in June.

The future
So, what challenges does Mr Riley believe lie ahead for himself and other primary care medicines management teams? He replies: “Without potential for a squeeze on NHS funding, the challenge of managing the prescribing budget will be key. PBC clusters need to consider how they can alter prescribing habits to support their investment in health outcomes without incurring dramatic increases in prescribing spend.” At the moment, the trust is basing 10 per cent of its prescribing budget on the NHS Prescribing Support Unit formula and 90 per cent on figures used historically. This may not be ideal, but Mr Riley believes that applying all the changes needed for the ideal situation in one fell swoop could cause huge disruptions (eg, quick movement of money from affluent areas to deprived areas could result in services being cut in some practices) and changes need to be phased.

However, “service rationalisation may be inevitable if costs are to be controlled.” Moving towards prescribing programme budgets will enable clusters to maintain financial control and limit the risk of such rationalisation, without compromising on quality,” he adds.

Prescribing budgets should not, however, only be a concern of primary care organisations and prescribers. Mr Riley says: “Prescribing budgets can also contribute to budget management by supporting adherence and hospital pharmacists play a key role in influencing secondary care prescribers and supporting areas pre- scripting committees. Medicines use reviews and medication reviews could enable prescribing changes. Moreover, he says that many primary care trusts have been looking at modifying the M U R principle. Some see limiting reviews to one year as a weakness. Another example from Stoke is that patients prescribed medicines for osteoporosis and needing help with their medicines are now referred to a community pharmacist for dedicated support for adherence, with up to three interactions allowed. ‘It doesn’t sit well within the NHS to talk about money much but we need to talk about it to get it in order. You’ve got to manage it to make it work. It won’t manage itself,’” he concludes.

Andrew Riley will be available online to answer questions on the topic of this article until 6 june 2009.

www.pjonline.com
Needle and syringe programmes: the basics

Graham Parsons examines the new National Institute for Health and Clinical Excellence guidance on needle and syringe programmes and looks at key points that pharmacists need to be aware of when offering these services.

It is 23 years since the first needle and syringe programme (NSP) began to operate from a pharmacy. Community pharmacies are now responsible for about 70 per cent of all needle exchanges in the UK and NSPs operate from about 1,900 pharmacies. NSPs represent a well-established service in a number of primary care organisations and are now supported with National Institute for Health and Clinical Excellence guidance.

Harm reduction

The principles of harm reduction are key to understanding the philosophy behind NSPs. Harm reduction refers to policies, programmes and projects that aim to reduce the health, social and economic harms associated with the use of psychoactive substances. It is an evidence-based and cost-effective approach bringing benefits to the individual, the community and society. The key principles are:

- Pragmatism — reduction of drug-related harms is a more feasible than eliminating drug use
- A hierarchy of goals
- Acceptance that the drug user has a choice and neither condemnation of or support for drug use
- To focus on reducing risks and harm
- Not to focus on abstinence but to support those who wish to moderate or reduce their drug use
- To maximise the range of intervention options

Figure 1 (p618) illustrates the hierarchy of harm reduction in relation to drug use. Such prioritisation of goals can equally be applied to other outcomes of treatment, such as physical and psychological health and social functioning. Service users should be encouraged to move up the hierarchy of harm reduction with practical advice and support from the multiagency network, which includes pharmacies, drug services and social care.

The scenario of a patient collecting syringes while receiving opioid substitution treatment can be understood within the philosophy of harm reduction. Pharmacy staff should recognise that the service user may have already made real steps to reduce his or her frequency of injecting. They should also be aware of confidentiality issues. NSPs and opioid substitution therapy are separate schemes and if a patient on opioid substitution is collecting syringes, it would be a breach of confidentiality to contact his or her prescriber or key worker. Genuine concerns for a client’s health should be discussed with the client initially and can be shared with the prescriber and key worker as part of a shared care management approach. Use of street drugs may indicate that the patient’s opioid dose is not high enough or that treatment is deteriorating and it is hoped that NSP providers would form a relationship with patients such that these issues could be discussed.

Evidence base for NSPs

NSPs began in response to the emergence of HIV and reducing the risk of individuals contracting blood-borne viruses (BBV) infections, and spreading these to others remains a main harm reduction priority. Current estimates suggest that in the UK one in two intravenous drug users have hepatitis C and one in 90 have HIV. A review of NSPs concluded that there is evidence to support their effectiveness in reducing HIV infection but there is insufficient evidence to determine the impact of NSPs on hepatitis C infection. This may be because hepatitis C appears to have been present long before structured NSPs were in place. The limited evidence for hepatitis C infection includes that from a Dutch study, which suggests that combining methadone treatment with full participation in NSPs can reduce the incidence of both HIV and hepatitis C.

Evidence also suggests that participation in NSPs can reduce risky behaviour among intravenous drug users, such as sharing of needle and syringes, and high frequency of injection although the evidence is less clear on the sharing of other paraphernalia.

Coverage "Coverage" is a term used throughout the NICE guidelines. It has three different mean-
NSPs usually associated with drug services make UK and extended opening hours compared with A gateway for opioid substitution treatment ■ Signposting information for psychosocial services and prevention of site injuries ■ Access to BBV testing and vaccination services ■ Signposting information for psychosocial services (eg, counselling, housing, child care) ■ A gateway for opioid substitution treatment

Information on safer injecting practices, including overdose prevention Information on safe disposal of equipment An advice and treatment service for injection site injuries Information on transferring from injecting to smoking Access to BBV testing and vaccination services Signposting information for psychosocial services (eg, counselling, housing, child care) A gateway for opioid substitution treatment

Figure 1: Hierarchy of harm reduction in drug use

Pharmacies ideal vehicles for the delivery of harm reduction. With an estimated 14 million face-to-face contacts a year, pharmacy staff also have many opportunities to engage with service users. It is also clear from the evidence that the service provided by pharmacies is welcomed by intravenous drug users. A number of reviews have demonstrated that pharmacies are popular, especially in relation to accessibility. However, challenges remain for pharmacies providing NSPs specifically in relation to:

- Embarrassment related to accessing equipment in a “public” environment (particularly experienced by women)
- Negative staff attitudes
- Maintenance of privacy and confidentiality for those collecting needles and receiving opioid substitution treatment
- Specialist NSPs being rated higher for advice and information than pharmacy-based ones

NICE recommendations
Six recommendations from NICE explain how to optimise the provision of NSPs to intravenous drug users. The first emphasises that a planning process, including a needs assessment and community engagement programme, should occur when NSPs are developed. Pharmacies planning to offer a service should engage with their local pharmaceutical committees and local drug partnerships to ensure they are an integral part of this needs assessment. Pharmacies should also be aware of the numbers of intravenous drug users and prevalence of BBVs in their areas (if figures are available) so opportunities for providing extra services are not missed. This information should be used as part of a comprehensive tool when commissioners map NSPs.

The second recommendation discusses meeting need. NICE recognises the need for a suite of services (including pharmacies) to engage different groups of intravenous drug users with a range of services and advice. Aims include increasing coverage, increasing use of NSPs, ensuring a range of syringes and needles are available, developing an effective needle and syringe disposal service, and making an advice, service and referral system (with appropriate integrated pathways).

The third recommendation expands on recommendation 2 by classifying levels of service, as described in Panel 1. Using a needs assessment process will allow local pharmaceutical committees and commissioners to commission specific services from pharmacies, either as part of a generic NSP or as a higher level service. It also emphasises the important role of pharmacy as a provider of extended hour services — an area that commissioners are keen to engage with to increase availability of NSPs within their local drug partnerships.

The fourth NICE recommendation considers equipment and advice. It emphasises that needles and syringes should not be dispensed to an “arbitrary limit” but should meet the needs of the user. For example, although a heroin user may require equipment to inject three or four times a day a stimulant user may require substantially more...
Panel 1: Levels of service

Level 1 Distribution of injecting equipment, either loose or in packs, with written information on harm reduction (eg, on safer injecting or overdose prevention).

Level 2 Distribution of “pick and mix” (bespoke) injecting equipment plus health promotion advice (including advice and information on how to reduce the harms caused by injecting drugs).

Level 3 Level 2 plus provision of, or referral to, specialist services (eg, vaccinations, drug treatment and secondary care).

Panel 2: Needle stick injuries

The risk of infection following injury through the skin, especially deep penetrating injuries involving a needle or a device visibly contaminated with blood, has been estimated at one in three for hepatitis B, one in 30 for hepatitis C, and one in 300 for HIV.9

Between 1997 and 2007 there were 14 cases of hepatitis C virus seroconversion in healthcare workers following percutaneous exposure and five cases of HIV seroconversion (none since 1999) in the UK. None of these was in pharmacy staff. Post exposure prophylaxis is available for HIV and hepatitis B exposure.9

If an individual receives a needle stick injury he or she should:

- Encourage the wound to bleed by squeezing it and holding it under cold water.
- Wash the affected area thoroughly with soap and water and cover the wound with a dry dressing.
- Dispose of the sharp safely in a clinical waste bin.
- Contact the nearest hospital casualty department immediately.

Panel 3: Examples of injecting equipment

- 1ml “diabetic” syringes Fine gauge and short needle, which is used for accessing fine veins, especially in arms and hands, or subcutaneous injecting.
- 2ml barrels Larger volume syringe suitable for attaching needle of choice.
- Sharps bin Used to dispose of contaminated injecting equipment. Small or large sizes available.
- Pre-injection swabs Used for injection control.
- Acidifiers Citric or ascorbic acid. Used to dissolve street heroin. Should be issued in sachets to reduce the risk of BBV contamination.
- Filters Used to filter particulate matter from the injection mixture.
- Water for injections (2ml or less) Legal to supply since July 2005, from sites operating an NSP. Available.
- Orange needles (25G x 1” or 25G x 5/8”) Narrow gauge and short needle. Commonly used for IV injection and injecting less fine substances, such as crushed tablets.
- Blue needles (23G x 1”) Wider gauge, longer needle. Generally used for intramuscular injection and for injecting into larger or deeper veins.
- Green needles (21G x 1.5”) Very wide gauge, very long needle. Suitable for intravenous injection (eg, steroids) and for accessing deep veins (eg, femoral vein in the groin).

Best practice

The NICE guidance is welcome and provides a supportive framework for the commissioning and operation of NSPs. However, it does not detail the gold standard operational protocol for a community pharmacy NSP, which includes training, service level agreements (SLAs), and health and safety.

Training

Providers of an NSP service should have training criteria to fulfil before accreditation by commissioners or governance forums. This will usually involve a core national training package (eg, “Substance use and misuse” from the Centre for Pharmacy Postgraduate Education) and will often be supported with local training that links with the local service provision and needs assessment. Such local training is integral because it will provide training to pharmacy staff who do not have access to any national training programme but who deal with most of the needle exchanges in the pharmacy. In England and Wales, training may also be linked into core competencies for NSP enhanced services.6

Service level agreement or operational policy

Pharmacies providing NSPs and local commissioners should ensure that a local operational policy or SLA is in place to clarify roles and responsibilities for the commissioner and provider. This should clearly define the service arrangements, accreditation and training requirements, data collection arrangements (see below), quality indicators, audit arrangements, clinical governance arrangements and remuneration. The Pharmaceutical Services Negotiating Committee has developed a template service specification which can be used for this purpose.7

Signposting and referral service

The NICE guidelines highlight the importance of NSPs in introducing intravenous drug users to other agencies...
for opioid substitution treatment and harm reduction interventions, such as BBV services. Optimal NSPs operating from community pharmacies will have a comprehensive signposting service with supporting literature outlining other services in the area. Pharmacy staff should have an understanding of the services available and how people can access them. A referral system could be incorporated within the SLA for pharmacies to refer intravenous drug users to three other agencies.

Health and safety Providers of a community pharmacy N SP should make risk assessments and staff at risk of needle stick injuries should be provided with hepatitis B vaccination. The provision of hepatitis B vaccination for pharmacy staff remains a local commissioning issue (some commissioners will fund vaccinations but others will not) but NICE expresses that they should have access to it.

Pharmacies should also have standard operating procedures in place with regard to sharps safety, dealing with needle stick injuries and the return of used injecting material. The risk of needle stick injury remains low if basic health and safety advice is followed. Panel 2 describes the risks associated with needle stick injuries and how to manage them.

Injecting equipment The optimal community pharmacy N SP will provide a broad range of injecting equipment to meet the needs of the local intravenous drug using population. Pharmacy staff should also be knowledgeable in the application and use of the equipment. However, staff should refer intravenous drug users to level 3 services if the advice sought falls outside their competency or they do not have the equipment available. Panel 3 lists a range of equipment that may be available from community pharmacy N SPs, and their applications.

Inntravenous drug users should always be encouraged to return used equipment in a sharps bin and given advice on how to dispose of needles and syringes safely. However, supply of clean injecting equipment must not be refused if they do not return used equipment.

The estimated number of syringes returned to N SPs will be one of the measures for the needle exchange monitoring system (N EX M S; see below).

Data collection arrangements Data collection helps local public health units to understand the demographics of intravenous drug users in a particular primary care organisation and its requirements. From April 2008 the National Treatment Agency for Substance Misusers has introduced an N EX M S that will also feed into this process. This aims to:

- Identify trends in hepatitis C transmission
- Provide better estimates of prevalence and incidence
- Measure the effectiveness of prevention measures, such as N SP and related harm reduction interventions
- Provide information to inform needs assessment

Action: practice points Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist’s CPD portfolio.
1. Read “Needle and syringe programmes: providing people who inject drugs with injecting equipment” and consider.
2. If your local drug partnership undertakes a needs assessment and if the community pharmacy network is involved.
3. If extended hours pharmacies are involved in providing a comprehensive service?
4. If the range of injecting equipment meets the needs of the intravenous drug user population?
5. If there is a local training plan to meet the needs of pharmacy staff.
6. Contact a local agency in the harm reduction sector. Ask if you can visit it to gain more understanding of its role.
7. Consider how you will respond the next time a service user who is receiving opioid substitution asks for a needle exchange in the pharmacy.

Evaluate For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

Pharmacy staff should be aware of the importance of data collection and how to record local information.

The future for community pharmacy NSPs Harm reduction has always been a prominent aspect of enhanced pharmacy services and level 3 services have already been available in some pharmacies. These include:
- An antibiotic patient group directive in Cornwall
- Wound care clinics in Sheffield
- A trial of BBV testing in Lincolnshire in 2005

This month, a pilot was launched across five primary care trusts, coordinated by the Hepatitis C Trust, to offer dry blood spot testing for hepatitis. Participating pharmacies are being paid between £10 and £15 per test.

The challenge for pharmacy is to promote its unique advantages to commissioners and public health units in order to expand level 3 services throughout the UK. The requirement for a comprehensive needs assessment and the recognition by NICE that pharmacies can provide extended services can be a driver for this evolution but community pharmacies need to grasp the opportunity.

References

CPD articles are commissioned by the Journal and are not peer reviewed.

Author Graham Parsons will be available online to answer questions on our CPD article until 6 June 2009.
Neuraminidase inhibitors: widespread use for influenza may reveal more adverse effects

The neuraminidase inhibitors (NAIs), oseltamivir (Tamiflu) and zanamivir (Relenza), are indicated for prophylaxis and treatment of influenza. Both antivirals are included within the current UK Health Protection Agency guidance for the treatment and prophylaxis of infection from the novel swine influenza A (H1N1) virus. These drugs are more effective and safer than older antivirals, such as the amantanes (amantidine and rimantadine). In the event of a global pandemic the NAIs will be administered to a large proportion of the population.

Common adverse effects: A recent review of the safety of NAIs for influenza examined the treatment and prophylactic dosing schedules in both children and adults. In addition, the Cochrane Collaboration reviewed the use of NAIs in both adults and children. For treatment of influenza, limited trial evidence indicates adverse events do not occur with a frequency greater than with placebo.

Osteltamivir: Clinical trials of oseltamivir for influenza prophylaxis in adults have shown nausea (10.5 per cent), vomiting (3 per cent), bronchitis, insomnia and vertigo to be common, and reported at similar rates to placebo. Nausea occurred at a statistically significant higher rate than placebo (5.6 per cent) and is dose related. When used to treat children, oseltamivir caused similar reactions to those in adults. Vomiting occurred in 14.8 per cent of children, and was statistically different from placebo (9.3 per cent).

In children receiving the once daily prophylactic dose, the incidence of vomiting is halved. Few children withdraw from therapy because of adverse events. There is no evidence that oseltamivir affects respiratory function or triggers asthma exacerbations.

Skin reactions may be associated with oseltamivir. Dermatitis, rash, urticaria, and eczema have been reported, although some reports were confounded by other drugs known to be associated with hypersensitivity reactions. The summary of product characteristics (SPC) of oseltamivir in adults states that dermatological reactions have occurred in up to 2 per cent of patients.

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ADVERSE DRUG REACTIONS

Oseltamivir also notes rare serious skin reactions, including Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis and angioneurotic oedema, although the frequency is unknown.

Zanamivir

Studies of zanamivir report primarily minor transient upper respiratory tract and gastrointestinal symptoms (ie, nausea, diarrhoea and sinusitis) as common adverse effects occurring with similar frequency to placebo in both adults and children. A Cochrane review did not identify any reports of zanamivir-related bronchospasm in children, although the zanamivir SPC describes rare reports of acute bronchospasm or serious declines in respiratory function, or both. These mainly occurred in patients with a previous history of respiratory disease. Zanamivir is not currently recommended in children or adults with severe asthma or chronic pulmonary disease because of the perceived risk of bronchospasm associated with its use. Short-acting bronchodilators should be available if it is used in those with less severe respiratory disease.

Neuropsychiatric effects

Concern has been expressed about the risk of neuropsychiatric events associated with both NAIs. Concerns first arose in Japan, where 76 per cent of all prescribed oseltamivir worldwide was used between 1999 and 2007. Cases (mostly from Japan) of delirium and abnormal behaviour leading to injury have been reported in patients with influenza who were receiving oseltamivir, in some cases resulting in fatal outcomes. Toovey et al reviewed 3,051 spontaneous reports of neuropsychiatric events (in 2,466 patients) reviewed 3,051 spontaneous reports of neuropsychiatric events in 2,466 patients). They estimated that 48 million doses of the drug had been prescribed worldwide during that period, with 91 per cent of adverse effect reports originating from Japan. Most events were in males (78 per cent) and within the first two days of treatment; 73 per cent of events occurred in those under 16 years of age.

The most commonly reported events were abnormal behaviour (n=1,160), delusions or perceptual disturbances (n=661), miscellaneous psychiatric reactions, depressed levels of consciousness (n=183), delirium (n=176) and convulsions (n=138). Of 16 suicidal events reported, 14 occurred in people over 16 years old. Of three successful suicide attempts, all occurred in adults with significant confounding factors.

Epidemiological studies have shown no association with neuropsychiatric events. A retrospective study of patients with influenza comparing those prescribed oseltamivir for treatment of influenza (n=3,211), with those not (n=19,985), found no association with neuropsychiatric events. Three epidemiological studies using US databases have also shown no association between oseltamivir and neuropsychiatric events. However, as with any observational pharmacoepidemiological study, the limitations in terms of confounding and bias should be considered.

Ascertaining whether NAIs are associated with neuropsychiatric events is confounded by the neuropsychiatric symptoms of influenza, which can have a similar onset as the case reports of problems with these drugs. A UK General Practice Research Database study showed increased risk of delusions, panic attacks, depressed consciousness and cognitive disturbances in influenza patients compared with the general population.

Regulators have taken a cautious approach. In February 2007 the European Medicines Agency’s Committee for Medicinal Products for Human Use recommended an update of the product information for oseltamivir to inform healthcare professionals and patients about the risk of neuropsychiatric side effects. Similar action was taken by the US Food and Drug Administration in February 2008. Currently, the UK SPC for oseltamivir notes the risk of neuropsychiatric disorders with influenza and the occurrence of post-marketing reports of convulsions and delirium, which have in some cases led to accidental injuries and death. It is also noted that most reports were in children and adolescents, with a rapid onset and resolution or adverse reactions. The lack of clear causality is stressed. A similar warning exists in the zanamivir SPC.

Summary

Both oseltamivir and zanamivir are safe drugs with relatively few adverse effects based on clinical trial data. A theoretical risk of bronchospasm with the use of inhaled zanamivir is of concern in those with respiratory disease and there is an unknown risk of very rare skin reactions to oseltamivir. Despite the concerns about neuropsychiatric events with the use of NAIs, and the inclusion of these in product literature, pharmacoepidemiological studies and case report analysis cast doubt on such an association. Influenza infection is arguably the more plausible cause of neuropsychiatric events. Widely spread use of NAIs, either for treatment or prophylaxis, may uncover further rare adverse reactions.

Oseltamivir is currently a black triangle drug, under intensive surveillance by the Medicines and Healthcare products Regulatory Agency. All suspected adverse reactions, including non-serious ones, should be reported, even if the reaction is well recognised, or if the reporter is uncertain that the drug has caused it. In addition, any suspected adverse reactions in children to either drug should be reported to the MHRA via the Yellow Card Scheme.

The MHRA website (www.mhra.gov.uk) can be visited for the latest advice.

— A nthony Cox, Asthma Pharmacy School, Birmingham, and D ebora Layton, Drug Safety Research Unit, Southampton.

References